Human Papillomavirus and Oropharyngeal Carcinoma in Indigenous Australians

Sneha Sethi

BDS, MDS (Oral Pathology, Microbiology and Forensic Odontology)

Submitted in fulfilment of the requirements for the degree of

Doctor of Philosophy in Dentistry

Adelaide Dental School
Faculty of Health and Medical Sciences
The University of Adelaide
Australia

Supervised by:

Prof. Lisa Jamieson
Adelaide Dental School
Faculty of Health and Medical Sciences
The University of Adelaide
Australia

Dr Xiangqun Ju
Adelaide Dental School
Faculty of Health and Medical Sciences
The University of Adelaide
Australia

October, 2021

Declaration

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

I acknowledge that copyright of published works contained within this thesis resides with the copyright holder(s) of those works.

I also give permission for the digital version of my thesis to be made available on the web, via the University's digital research repository, the Library Search and also through web search engines, unless permission has been granted by the University to restrict access for a period of time.

I acknowledge the support I have received for my research through the provision of an Australian Government Research Training Program Scholarship.

Signed: … …….

Sneha Sethi (Candidate)

Date: 12/10/2021

Table of Contents

List of Figures

List of Tables

Keywords

Human Papillomavirus

Indigenous health

Oral health

Oropharyngeal cancer

Indigenous Australians

Screening tools

Natural history

Oral cancer

Persistence

Clearance

Heck’s Disease

HPV16/18

Mixed methods

Qualitative research

List of Abbreviations and Acronyms

ACCHO – Aboriginal Community Controlled Health Organisations

ACIP – Advisory Committee on Immunization Practices

AJCC – American Joint Committee on Cancer

ATPase – Adenosine Triphosphate Enzyme

CI – Confidence Intervals

CLE – Confocal Laser Endomicroscopy

DCOHS – Dental Care and Oral Health Study

DNA – Deoxyribonucleic acid

DNA ISH – Deoxy ribonucleic Acid – In-situ Hybridization

DTA – Diagnostic test of Accuracy

ENTREQ – Enhancing transparency in reporting the synthesis of qualitative research

EQ-5D – European Quality of Life indicator or EuroQol

EV-HPV – Epidermodysplasia verruciformis Human Papillomavirus

FDA – U.S. Food and Drug Administration

HCC – Health Care Card

HPV – Human papilloma Virus

HPV-OPC – Human Papillomavirus – Oropharyngeal Carcinoma Study

hrHPV – High-risk HPV

HRQoL – General health related quality of life

HSROC – Hierarchical summary receiver-operating characteristic

IHC – Immunohistochemistry

IPVS – International Papillomavirus Society

JBI – Joanna Briggs Institute

MANOVA – Multivariate analysis of variance

MEDLINE – Medical Literature Analysis and Retrieval System Online

mRNA – Messenger Ribonucleic Acid)

NACCHO – National Aboriginal Community Controlled Health Organisation

NHRMC – National Health and Medical Research Council

NIH – National Institute of Health

NS – Not Specified

OHIP-14 – Oral health Impact Profile

OHRQoL – Oral health related quality of life

OPSCC – Oropharyngeal squamous cell carcinomas

OSCC – Oral squamous cell carcinoma

PCR – Polymerase Chain Reaction

PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-Analyses

ROC – Receiver Operating Characteristic Curve

RR – Risk Ratio

SEM – Social Ecological Model

SES – Socio-economic Status

SR – Systematic Review

SUMARI – System for the Unified Management, Assessment and Review of Information

TAFE – Technical and Further Education

TNM – Tumor (T), nodes (N), and metastases (M)

WHO – World Health Organisation

List of Symbols

% – Percentage

* – P<0.05

≥ – great than or equal to

i.e. – For example

N – Sample size

- – Not available

Thesis Abstract

Current trends suggest that the prevalence of oropharyngeal squamous cell carcinomas (OPSCC) associated with human papillomavirus (HPV) is increasing. Although Indigenous Australians have high rates of OPSCC, the incidence of oral HPV and the associated risk factors in this group are unknown. This thesis is an embedded component of a larger NationalHealth and Medical Research Council (NHRMC) funded project titled 'Human Papillomavirusand Oropharyngeal Carcinoma amongst Indigenous Australians'. This thesis primarily exploresthe prevalence of HPV infections, accompanied by a qualitative insight regarding awareness and prevention strategies amongst Indigenous populations.

The thesis is broadly divided into seven sections, with each section comprising twelveChapters.

Section A is an introduction of the thesis and includes Chapter 1, which is an overview of HPV, oropharyngeal carcinoma, and cancer burden amongst Indigenous Australians. Chapter 2 includes a review of the literature summarizing the prevalence of oral HPV amongst Indigenous populations globally and the prevalence of high-risk HPV infections amongst Indigenous populations. The Chapter concludes by highlighting identified gaps in research, followed by the aim and a basic outline of this thesis.

Section B comprises Chapter 3, which describes the objectives of the larger HPV project and outlines the nested aims and expected contributions covered in this thesis. It describes the methodology and study design highlighting the research questions explored.

Section C includes Chapter 4, which comprises comparative research highlighting the general health and oral health inequalities faced by Indigenous Australians. It includes analyses of the data collected as a part of the broader HPV project.

Section D comprises three Chapters (Chapters 5 to 7), which provide details of HPV infection more broadly among Indigenous Australians. Chapter 5 is a systematic review and meta-analysis on the prevalence of HPV infection amongst Indigenous Australians. Chapter 6 is an analysis of the risk factors associated with incidence, persistence, and clearance of oral HPV infection at 12 months, as observed in the HPV project. Baseline findings of the HPV project showed an unexpectedly high prevalence of HPV 13 and 32, which are frequently associated with Heck's Disease (asymptomatic, benign neoplastic condition caused by HPV 13 or 32). Chapter 7 is a critical review of literature for Heck's disease and provides an insight into the age, sex, clinical presentation, genetic predisposition, ethnic association, global burden, and available treatment strategies.

Section E is the qualitative component of this thesis, and includes Chapters 8 and 9. Chapter 8 addresses the high risk of Indigenous populations at a global level in experience of both HPV infection and HPV-related cancers. It presents a social-ecological model of HPV infection awareness and cervical cancer prevention among Indigenous women, offering a holistic and practical approach for Indigenous health policymakers. Chapter 9 is the psychological evaluation of the different emotions felt by Indigenous participants after hearing about cancer in the family or community. It discusses the critical importance of psycho-oncology, and the considerations for Indigenous peoples.

Section F includes Chapter 10, involving the discussion of future objectives arising from this research. Clinical examinations are to be included in the next phase of this project and this Chapter is a proposition of using confocal imaging as a suitable screening tool and its diagnostic test of accuracy.

This thesis identifies the general and oral health inequalities faced by Indigenous Australians, and the increased burden of HPV infection and its associated carcinomas. An ethnic

predisposition to Heck's disease was identified with a large proportion of affected people having an Indigenous origin. The qualitative component identified a large gap regarding the awareness and prevention of HPV infection amongst Indigenous populations. It also produces a model to address this gap at an individual, family, community, and system level. The psycho-oncological evaluation demonstrated that, for Indigenous peoples, the experience of cancer care is complex as the health of an individual is determined by the emotional, cultural, social, and physical well-being of an entire community. The diagnostic test of accuracy for confocal laser endomicroscopy shows exceptionally high sensitivity and specificity for diagnosing oral squamous cell carcinoma. The next step would be its transference to a clinical setting and its adaptation as a portable tool for screening of oropharyngeal cancer amongst Indigenous Australians.

Acknowledgements

"We all are visitors to this time, this place. We are just passing through. Our purpose here is to observe, to grow, to love and then we return home" – Australian Aboriginal Proverb

First and foremost, I would like to acknowledge that the land on which this research was undertaken is the traditional lands for the Kaurna people and that I respect their spiritual relationship with their Country. I also acknowledge the Kaurna people as the traditional custodians of the Adelaide region and that their cultural and heritage beliefs are still as important to the living Kaurna people today. I will be forever thankful to the traditional custodians for allowing me to perform my research on their beautiful country and I vow to always respect and gratify the culture and tradition bestowed upon me.

Second, I want to express my sincere heartfelt gratitude to my supervisory panel led by Professor Lisa Jamieson and co-supervisor's Dr Xiangqun Ju, for their experienced professional guidance, continuous support, encouragement, insightful comments, immense knowledge, patience, and motivation.

I am deeply indebted to Lisa, my principal supervisor, for allowing me to be part of the National Health and Medical Research-funded national project, which provided a great platform for me to grow. Lisa has been a great mentor and advisor by giving me invaluable professional and personal advice, helping to shape and polish my ideas, pushing me beyond my comfort zones, influential guidance, and constant encouragement to make most of the opportunities in front of me. Lisa has put her faith and trust in me, on more than one occasion. I hope I have never let her down and also look forward towards a bright future working together. She has been the family and guardian any one would wish for, in a foreign land and a brand-new challenging role. Thank you, Lisa.

I am extremely grateful to Xiangqun, my co-supervisor, for spending time with me regularly going through her suggestions for the project, publications, and the thesis. Her great attention to detail, countless reading of my drafts and timely feedback enabled me to stay on track. I consider myself very blessed to have such a wonderful and supportive supervisory panel each with their own unique research and academic expertise, and I think I could not have gotten through it without their constant support and guidance.

Third, thanks also go to other chief investigators and principal investigators in the HPV project and co-authors, Prof Gail Garvey, Prof Karen Canfell, Prof Megan Smith, Dr Annika Antonsson, Prof Richard Logan and Ms Joanne Hedges for their valuable input, detailed and timely feedback and guidance given throughout the duration of the project. Joanne has been a great support by guiding me through the culturally appropriate methodology while performing field work and ethical research. Her diligence and passion for the work has left a lasting impression on me, and I have learnt tremendously from spending time with her. I cannot thank her enough for giving me so much of her time, professionally and personally. I have learned a lot from Joanne and thank her for his flexibility, patience and feedback. Overall, it was a good learning experience and great professional opportunity for me to work with, learn from, and listen to all these researchers and I highly value this life changing experience.

Fourth, I would like to express my deep gratitude for the partnership, involvement and support from the following Aboriginal Community Controlled Health Services and community organisations, without whom none of this research would be possible: Yadu Health (Ceduna), Moorundi ACCHS (Murray Bridge), Pika Wiya Health Service Aboriginal Corporation (Port Augusta), Umoona Tjutagku Health Service Aboriginal Corporation (Coober Pedy), PLAHS - Port Lincoln Aboriginal Health Service (Port Lincoln), Pangula Mannamurna (Mount Gambier), Tarpari Wellbeing Centre (Port Pirie), Nunyara Aboriginal Health Service (Whyalla), Nunkuwarrin Yunti of South Australia (Adelaide), and Stepping Stones (Ceduna).

This gratitude reaches out to each one of the participants who are a part of the study, I would like to thank you for your time and trust in our team to make this possible.

Fifth, I express my gratitude to the past postgraduate coordinator (PGC), Prof David Brennan for his support and guidance in regards to my PhD application and managing a smooth start for me. I am extremely thankful to our current PGC, Dr Toby Hughes for his continued support and guidance throughout the journey.

I also thank the entire staff of the Australian Research Centre for Population Oral Health (Dr Liana Luzzi, Dr Sergio Chrisopoulos, Prof Loc Do, Dr Najith Amarasena, Dr Kostas Kapellas and Dr Manasi Mittinty, Sathvika Justine) and the administration staff (Ms Jacqueline Aldis, Ms Nikkita Dodds, and Ms Kimberly Walters) who have been supportive in every way possible. I appreciate Jacqueline Aldis, and Nikkita Dodds for all their support and feedback throughout the project. I am thankful to Jacki for coordinating the process to providing me access to the work-related data and Nikkita for her prompt and efficient resource based support.

I would like to acknowledge that my PhD candidature was funded by the University of Adelaide through Research Training Program Scholarship by the Commonwealth Government.

Acknowledgements also go to, Dr Pedro Henrique Ribeiro Santiago, Dr Davi Manzini Macedo, Dr Dandara Haag, Dr Young Ha Song and Dr Rahul Nair my post-doctoral icons for keeping their doors open and willingly helping out any time. Thanks to Pedro for his wonderful Network Analysis skills and for providing me the correct guidance for factor analysis and factor exploration, which I found very useful and time saving.

Special thanks from the bottom of my heart go to my fellow PhD colleagues and dear friends who were the core peer support system: Brianna Poirier, Anna Ali, Mehrsa Zakersharak, Emilija Jensen, Sonia Nath, Gustavo Hermes Soares and Arash Ghanbarzadegan, for their support, time, laughter, stimulating discussions and encouragement. Brianna and I have been

best friends since the first day we went to Ceduna for field work, which I believe has helped both of us get through this long journey. Thank you for holding my hand and walking me through the all the qualitative research in the thesis. I will always be grateful for Anna and her quantitative skill expertise, she has always been my first call in distress. A special shout out to my friends in the School of Public Health, Dr Blesson Varghese and Neha Lalchandani, who have been such a source of inspiration for me from the very beginning.

I finish with my family both here in Australia and India, and other countries where most of my support and energy comes from. I have been blessed with two sets of the most supportive and loving parents, my dad, mum, father-in law and mother-in law. My brother has been the greatest support and encouragement for me. I would also like to thank my brothers-in-law and sister-in laws for their constant support and a special mention of my nephews (Pratham and Aavir) for never failing to make me smile when I was down. My father–in law told me before I left for my PhD, “You can do it, and you should, we will always support you”; those kind words have always managed to give me strength when I needed it most. I am what I am because of my mum and dad, who have forever trusted me and gave me their company for many early mornings and late nights while I was working and when I needed their support. They have given up on many things to support me in all possible ways especially providing a listening ear. I am grateful to my parents for putting up with me all through this long journey even when I was irritable. Special thanks to the most important person in my life, Pratul. You have been by my side for the last 15 years and I do not think I could have achieved anything without the love and strength I get from you. I am forever grateful and thankful for the day you walked into my life and have always pushed me towards excellence, for you are the person who believed in me when nobody else did. Thank you Pratul.

A big thank you to everyone who has been a part of my PhD journey in one way or the other and whose names I may have missed out. This journey has indeed been a life changing

experience and an incredible one and I consider the skills I have gained to be an asset for my future endeavours.

Critical Reflexivity: Improving Aboriginal and Torres Strait Islander health is a global responsibility and I feel privileged to have been given an opportunity to work in this space. I am aware and conscious of my responsibilities associated with Aboriginal and Torres Strait Islander research. I understand the academic and clinical aspects of oral and oropharyngeal cancer, but I also acknowledge the equally critical social, ethical, and political implications of research in Aboriginal and Torres Strait Islander health. As a non-Indigenous person working in the Aboriginal and Torres Strait Islander health field, I feel a personal responsibility to place my research finding s appropriately in a cultural context. I am mindful of the disempowerment research has the potential to create, and also my commitment to return value to Aboriginal and Torres Strait Islander communities and avoid cycles of disempowerment being perpetuated, and an understanding of culturally safe research principles with Aboriginal and Torres Strait Islander people. I have had the privileged opportunity to be mentored by a senior Aboriginal researcher throughout my journey, closely followed and supervised by an Aboriginal Research Reference Group. I understand the responsibility I have in disseminating my research findings to community and envision myself working in this sphere of research for the rest of my career.

Sneha Sethi

October 2021

PUBLICATIONS DURING CANDIDATURE

Publications contributing to this thesis

Published:

1. **Sethi S**, Ali A, Ju X, Antonsson A, Logan R, Jamieson L. *An update on Heck's disease-a systematic review*. J Public Health (Oxford). 2021 Jan 27: fdaa256. doi: 10.1093/pubmed/fdaa256. Epub ahead of print. PMID: 33501985.
2. **Sethi S,** Ali A, Ju X, Antonsson A, Logan R, Canfell K, Smith M, Garvey G, Hedges J, Jamieson L. *A systematic review and meta-analysis of the prevalence of human papillomavirus infection in Indigenous populations - A Global Picture*. J Oral Pathol Med. 2021 May 18. doi: 10.1111/jop.13201. Epub ahead of print. PMID: 34008187.
3. **Sethi S**, Poirier B, Canfell K, Smith M, Garvey G, Hedges J, Ju X, Jamieson LM. *Working towards a comprehensive understanding of HPV and cervical cancer among Indigenous women: a qualitative systematic review*. BMJ Open. 2021 Jun 30;11(6): e050113. doi: 10.1136/bmjopen-2021-050113. PMID: 34193502.

Manuscripts under review:

4. **Sethi S**, Zakershahrak M, Santiago PHR, Jamieson LM, Brennan D. *General and oral health related quality of life among Indigenous and non-Indigenous Australians – A comparative research paper*. BMC Oral Health (Under Review, submitted April, 2021)
5. **Sethi S**, Ju X, Antonsson A, Canfell K, Smith M, Garvey G, Hedges J and Jamieson L. *Oral HPV infection among Indigenous Australians; incidence, persistence and clearance at 12-months follow-up.* Cancer Epidemiology, Biomarkers and Prevention (Under Review, submitted September 2021)
6. **Sethi S**, Ju X, Logan R, Sambrook P, McLaughlin R and Jamieson L. *Diagnostic Accuracy of Confocal Laser Endomicroscopy for the Diagnosis of Oral Squamous Cell*

Carcinoma: A Systematic Review and Meta-Analysis. International Journal of Environmental and Public Health (Under Review, submitted September 2021)

7. **Sethi S**, Ju X, Hedges J and Jamieson L. *Psycho-oncological considerations for Indigenous populations*, J Cancer Biology (Under Review, submitted September 2021)

Other relevant Publications/manuscripts:

8. Jamieson LM, Garvey G, Hedges J, Leane C, Hill I, Brown A, Ju X, **Sethi S**, Roder D, Logan RM, Johnson N, Smith M, Antonsson A, Canfell K. *Cohort profile: indigenous human papillomavirus and oropharyngeal squamous cell carcinoma study - a prospective longitudinal cohort*. BMJ Open 2021,11: e046928. doi:10.1136/bmjopen-2020-046928
9. Ju X, Canfell K, Smith M, **Sethi S**, Garvey G, Hedges J, Logan RM, Antonsson A, Jamieson LM. *High-Risk Human Papillomavirus-Related Oropharyngeal Squamous Cell Carcinoma Among Non-Indigenous and Indigenous Populations: A Systematic Review*. Otolaryngol Head Neck Surg. 2021 Jul;165(1):23-32. doi: 10.1177/0194599820975042. Epub 2020 Nov 24. PMID: 33228443.
10. Poirier B, **Sethi S**, Canfell K, Smith M, Garvey G, Hedges J, Ju X, Jamieson LM. HPV *Vaccine: Uptake and understanding among global Indigenous communities – A qualitative systematic review*. BMC Public Health (Under Review, submitted June 2021)
11. Du M, **Sethi S**, Nair R, Duan X. *Head and neck cancers survival prediction using machine learning algorithms and encompassing histopathology*. Oral Oncology (submitted December 2020)
12. Zakershahrak M, Santiago PHR, **Sethi S**, Haag DG, Brennan D, Jamieson LM. *Psychometric properties of the EQ-5D-3L in South Australia: a multi-method non-*

preference-based validation study. Current Medical Research & Opinion (Under Review, submitted July 2021)

PRESENTATIONS ARISING FROM THIS THESIS

Presentation Title	Conference/ Research Team
Oral Human Papillomavirus	Australian Research Centre for Population Oral Health, The University of Adelaide, Sept 2019
Oral cancer screening tool in Indigenous Populations	Institute of Photonics and Advanced Sensing, The University of Adelaide, December, 2019
Oral HPV in an Indigenous Australian population	33rd International Papillomavirus Conference, Barcelona, Spain (Virtual conference). 20-24, July, 2020
HPV in Indigenous populations: Qualitative and quantitative systematic reviews	Australian Research Centre for Population Oral Health, The University of Adelaide, Oct 2020
Natural History of Oral Human Papillomavirus in Indigenous Australians	Australian Society for Medical Research, South Australian Scientific Meeting, Adelaide, July 2021
Diagnostic Accuracy of Confocal Laser Endomicroscopy for the Diagnosis of Oral Squamous Cell Carcinoma: A Systematic Review and Meta-Analysis	15th Annual Florey Postgraduate Research Conference, September 2021
Working towards a comprehensive understanding of HPV and cervical cancer amongst Indigenous women: a qualitative systematic review	IRNet National Aboriginal and Torres Strait Islander Health Research Showcase (scheduled Nov, 2021)

SECTION A: INTRODUCTION

Overview of Section A

Section A provides an introduction to this thesis. It its broadly divided into five parts, the first provides an overview of the basic structural and functional details of Human Papillomavirus (HPV). The second provides an understanding of oropharyngeal carcinoma and its association with HPV. The third describes HPV vaccines and their development. The fourth describes Indigenous populations and the health inequalities faced. The final part of this section describes a gap in the existing research and concludes by presenting the main aim for the present research.

01

Introduction

1.1 PREFACE

Human papillomavirus (HPV) infection has been long recognised as a source of morbidity and mortality with distinct carcinogenic potential. There has been tremendous progress in understanding the structure of HPV and its pathogenesis. Most HPV infections (whether high risk or low risk) resolve without any medical intervention or treatments and go undetected. Persistent or progressive infections, however, remain difficult to treat. Human papillomavirus infection is one of the most common sexually transmitted diseases in the world, and cervical cancer still causes significant morbidity and mortality. However, OPSCC has now surpassed cervical cancer as the most common HPV-driven cancer[1].

Higher prevalence of risk factors, poor outcomes, and under-reporting are among the cancer control challenges for Indigenous peoples. Although Indigenous Australians have high rates of OPSCC, the prevalence and incidence of oral HPV infection and associated risk factors in this group are unknown. Understanding this important phenomenon and developing relevant preventive/adaptive strategies is the underlying rationale for this research.

This Chapter outlines the background to the body of research supporting this thesis and summarises the burden of HPV infections and associated cancers in Indigenous Australians. The Chapter concludes by outlining the overarching aims and the structure of the thesis.

1.2 BACKGROUND

Human Papillomaviruses (HPV) are a whole spectrum with a multitude of subtypes and variants. They have posed an enigma from initial discovery, with the implications still being evaluated and researched. HPVs are broadly divided into high and low risk types according to oncogenic potential[2]. HPV is considered the prime etiological agent of cervical cancers [3,4]. HPV has also been correlated with ano-genital, vulvar, penile and oropharyngeal carcinomas[4]. The incidence of HPV infection and its related cancerous and precancerous lesions aregoverned by many risk factors.[3-5] These include onset of sexual activity, multiple sexual partners, sexual practices, residential locations, age, and other demographic and socioeconomic factors. Nationwide surveys are currently underway to record the population-level prevalence of this virus and its consequences. According to one survey, high-risk HPV types were the most common sexually transmitted infection in Australia, with an estimated 4 out of 5 Australians having a high risk (HPV) infection at some point in their lives[6]. At a global level, there is speculation that Indigenous populations are at a higher risk for HPV infections and their sequelae due to a range of factors. There are currently no population evaluations of carriage of high-risk HPV (hrHPV) types in the upper aero-digestive tract among Aboriginal and Torres Strait Islander Australians[6]. This is a substantial deficit in the contemporary knowledge base, particularly given the higher risk for oropharyngeal cancer among this population. To determine prevalence of hrHPV, and risk factors associated with the infection among Indigenous populations, data on prevalence using sensitive HPV detection methods are necessary[6]. Also necessary are Indigenous Australian views and understandings of HPV infections, barriers to and facilitators of HPV vaccines, and community experiences of OPSCC.

1.4 REFERENCES

1. Tang et al. Oral HPV16 DNA as a screening tool to detect early oropharyngeal squamous cell carcinoma. Cancer Sci. 2020; 111:3854-386
2. Panatto D, Amicizia D, Trucchi C, et al. Sexual behaviour and risk factors for the acquisition of human papillomavirus infections in young people in Italy: suggestions for future vaccination policies. BMC Public Health. 2012; 12:623
3. Burd EM. Human papillomavirus and cervical cancer. Clin Microbiol Rev. 2003;16(1):1-17. doi:10.1128/CMR.16.1.1-17.2003.
4. Bansal A, Singh MP, Rai B. Human papillomavirus-associated cancers: A growing global problem. Int J Appl Basic Med Res. 2016;6(2):84-89. doi:10.4103/2229-516X.179027
5. Liu ZC, Liu WD, Liu YH, Ye XH, Chen SD. Multiple Sexual Partners as a Potential Independent Risk Factor for Cervical Cancer: a Meta-analysis of Epidemiological Studies. Asian Pac J Cancer Prev. 2015;16(9):3893-900.
6. Jamieson L, Garvey G, Hedges J, et al. Human Papillomavirus and Oropharyngeal Cancer Among Indigenous Australians: Protocol for a Prevalence Study of Oral-Related Human Papillomavirus and Cost-Effectiveness of Prevention. JMIR Res Protoc. 2018;7(6): e10503.
7. InformedHealth.org [Internet]. Cologne, Germany: Institute for Quality and Efficiency in Health Care (IQWiG); 2006-. Cervical cancer: Human papillomaviruses (HPV) 2012 Nov 21 [Updated 2017 Dec 14]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK279260/

02

Literature Review

2.1 HUMAN PAPILLOMAVIRUS

2.1.1 Introduction

Papillomaviruses are a group of DNA viruses which cause papillary or wart-like growths on the bodies of human and other animals[1]. There are more than 40 sexually transmitted types of HPV that infect the skin and mucous membranes[1]. In infected individuals, the immune system normally eliminates the virus within two years, but in some individuals, persistent HPV infection causes cervical cancer and genital warts (broadly categorised as high risk and low risk based on their oncogenic potential i.e. their ability to cause cancer)[2]. HPVs are not classified into serotypes but into genotypes on the basis of deoxyribonucleic acid (DNA) sequence[1,2].

2.1.2 *Structure and Functional characteristics*

The structural and functional characteristics of HPV are demonstrated in Figure 2.1 - 2.3 and Table 2.1

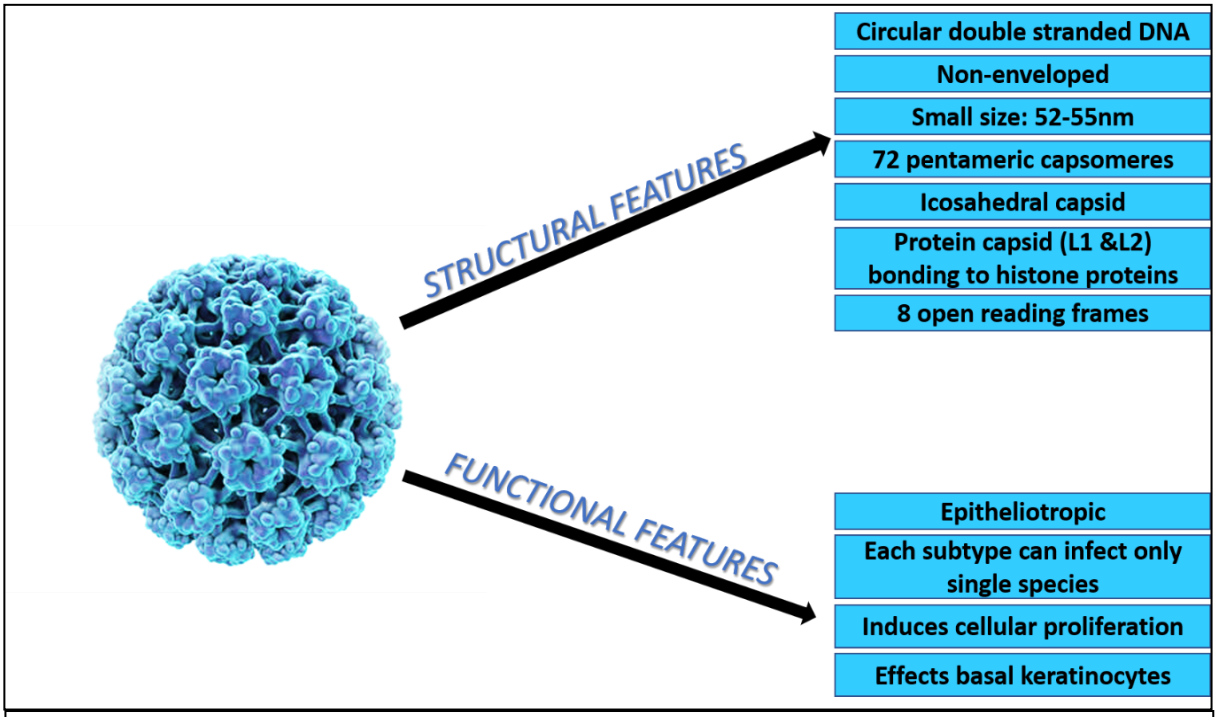


Figure 2.1: Structural and functional characteristics of HPV[1,2]

The virus comprises 8 open reading frames which form corresponding proteins, which are broadly divided into E (Early) and L (Late) types. Each component/protein has a distinct function in the lifecycle of this virus.

Table 2.1 - The basic structural and functional features of Human Papillomavirus[1-5]

E1#	• Factors that recognize the origin of replication • Ability of HPVs to establish their genome in basal cells relies upon it • Recognizes and binds to the viral origin of DNA replication as a hexameric complex • Necessary for viral DNA replication • Interacts with replication protein A (RPA), which results in the rapid stabilization of single-stranded DNA generated by E1 helicase activity Interaction with H1 histone plays a role in unravelling the viral chromatin by removing H1 histones before unwinding the DNA.
E2#	• Factors that recognize the origin of replication • Main regulator of viral gene transcription • Binds the viral transcriptional promoter as a dimer • Involved in viral DNA replication • Interacts with and recruits E1 to the origin • Ability of HPVs to establish their genome in basal cells relies upon it
E4#	• Involved in the late stages of the life cycle of the virus • Interacts with the keratin cytoskeleton and intermediate filaments • Localizes to nuclear domain 10 • Induces arrest in cell cycle at stage G2

	• Facilitates virus assembly and release - required for viral DNA amplification and expression of the L1 capsid gene (in Cottontail Rabbit Papillomavirus)
E5[#]	• Function during both early and late phases • Necessary and sufficient to induce suprabasal DNA synthesis (both E16 & 31) • Induces unscheduled cell proliferation • Interacts with 16k subunit C of vacuolar ATPase • Activates growth factor receptors and other protein kinases • Inhibits apoptosis and inhibits traffic of major histocompatibility complexes to the cell surface.
E6[#]	• Induces DNA synthesis • Induces telomerase • Prevents cell differentiation • Interacts with four classes of cellular proteins: transcriptional co-activators, proteins involved in cell polarity and motility, tumour suppressors and inducers of apoptosis primarily p53, and DNA replication and repair factors. • Target a number of negative regulators of the cell cycle, primarily p105Rb • Facilitate stable maintenance of viral episomes • Stimulate differentiating cells to re-enter the S phase • Ability of HPVs to establish their genome in basal cells relies upon it
E7[#]	• Targets a number of negative regulators of the cell cycle primarily p53 • Facilitates stable maintenance of viral episomes • Stimulates differentiating cells to re-enter the S phase • Ability of HPVs to establish their genome in basal cells relies upon it (in some cases)

	• Necessary and sufficient to induce suprabasal DNA synthesis (HPV 16) • Induces unscheduled cell proliferation • Interacts with histone acetyl transferases • Interacts with negative regulators of the cell cycle and tumour suppressors primarily p105Rb.
L1#	• Assemble the proteins in capsomeres which form icosahedral capsids around viral genome during the production of more virions • Major viral structural protein - assembles in capsomeres and capsids • Interacts with L2 • Interacts with cell receptor(s) • Encodes neutralizing epitopes

E1, E2, E4, E5, E6, and E7 - **S**ix early genes of the **HPV Genome**
L1 and L2 – Two late genes of the HPV genome

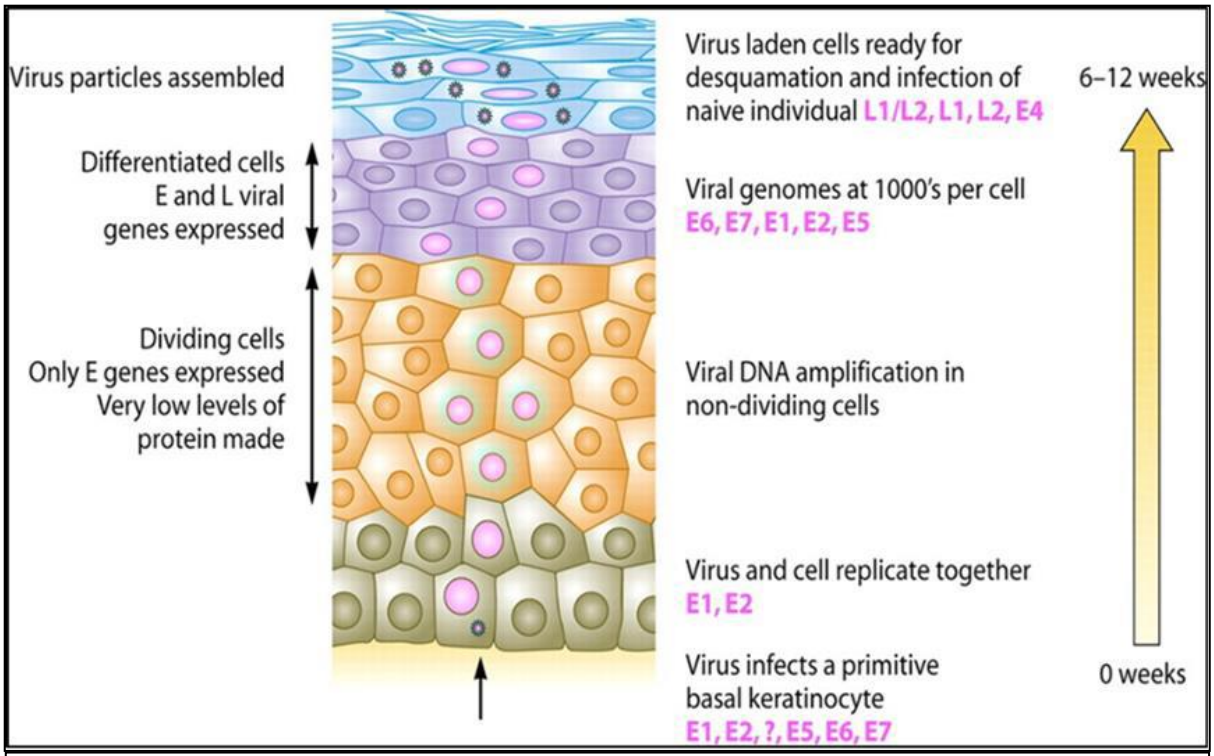
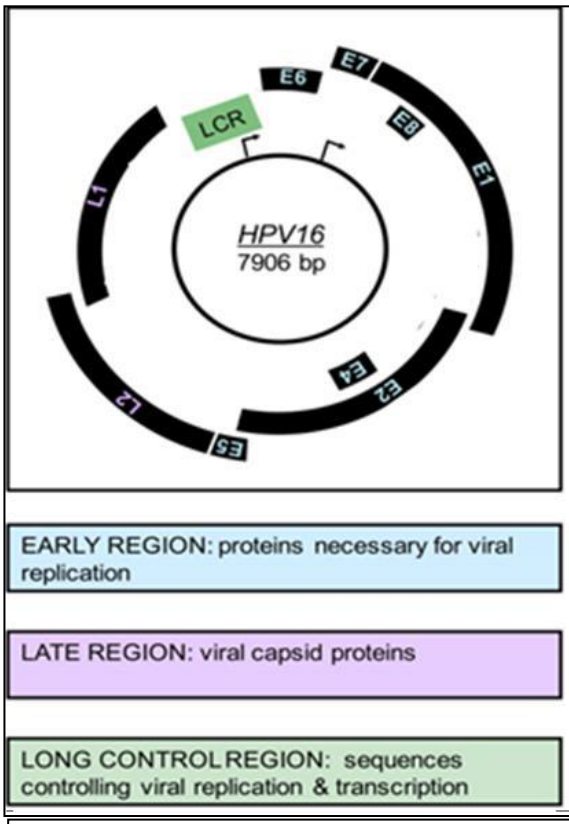


Figure 2.2: The replication cycle of high-risk HPV in a differentiating epithelium[3]



ORF	HPV16 PROTEIN FUNCTION
E1	origin binding protein, ATPase-dependent helicase involved in genome replication
E2	regulator of viral gene transcription, association with E1 (origin binding), viral genome partitioning
E4	expressed abundantly as E1^E4 fusion protein, cytokeratin network destabilization, virus release and transmission
E5	small transmembrane protein, interacts with EGF receptor activating mitogenic pathways
E6	drives cell cycle allowing genome amplification in upper epithelial layers, association with E6AP and degradation of p53, PDZ-protein binding, hTert activation
E7	drives cell cycle allowing genome amplification in upper epithelial layers, association with and degradation of pRB, mitotic mutator
E8	expressed as E8^E2 fusion protein, acts as a repressor of transcription and replication during the viral life cycle
L1	major capsid protein, assembles into pentameric capsids forming the icosahedral virion (prophylactic vaccines)
L2	minor capsid protein, involved in viral DNA encapsidation, facilitates viral entry and trafficking

Figure 2.3: Functions of HPV Genes and their proteins[5]

2.1.3 HPV Genus Branches

The traditional HPV taxonomic system included types, with each genetic variant considered a subtype. The modern taxonomic system has depicted the categorisation in the form of a large tree with major and minor branches. The major branches, also referred to as the genus or genera, are usually identified by Greek letters. The minor branches depict the subtypes with biological similarities and differences in the genetic makeup. A detailed description of different major branches or genus are tabulated in Table 2.2.

Table 2.2 Description of different major branches or genus of human papillomavirus[2-5]

Alpha-papillomavirus	Mucosal and cutaneous lesions in humans and primates. High- and low-risk classification based on molecular biological data: high-risk types (pre- and malignant lesions) immortalize human keratinocytes;

	low-risk types (benign lesions) do not. Recent compilations of epidemiological data demonstrate more frequent association of specific species at high-risk types.
Beta-papillomavirus	Cutaneous lesions in humans, Infections exist in latent form in general population, activated under conditions of immune suppression. Also referred to as EV–HPV types due to close association with disease Epidermodysplasia verruciformis (EV).
Gamma-papillomavirus	Cutaneous lesions in humans, Histologically distinguishable by intracytoplasmic inclusion bodies specific for type species
Delta-papillomavirus	Lesions in ungulates, Induces fibro-papilloma's in the respective host. Trans-species transmission occurs inducing sarcoids.
Epsilon-papillomavirus	BPV; cutaneous papilloma's in cattle
Zeta-papillomavirus	Cutaneous lesions in horses
Eta-papillomavirus	Avian papillomaviruses, Cutaneous lesions in host
Theta-papillomavirus	Avian papillomaviruses, Cutaneous lesions in host
Iota-papillomavirus	Rodent papillomaviruses, Cutaneous lesions
Kappa-papillomavirus	Isolated from rabbits, Cutaneous and mucosal lesions
Lambda-papillomavirus	Animal papillomaviruses, Benign mucosal and cutaneous lesions

Mu-papillomavirus	Human papillomaviruses, Cutaneous lesions, Histologically distinguishable by intracytoplasmic inclusion bodies specific for type species
Nu-papillomavirus	Human papillomavirus, Benign and malignant cutaneous lesions
Xi-papillomavirus	Bovine papillomaviruses, Induce true papilloma's in host. Cutaneous or mucosal lesions
Omicron-papillomavirus	Isolated from hamsters, Mucosal lesions
Pi-papillomavirus	Isolated from hamsters, Mucosal lesions

Table 2.3 Chronological evolution of HPV from 400BC until 2020 [6-59]

400 BC	*Hippocrates* describes Warts as a disease. Hence, the first mention of papilloma-like growths and their characteristics in the history of medical sciences.
1842	***Dr Rigoni Stern*** suggests a link between sexual activity and the incidence of cervical cancer; and hypothesizes an infectious association between the two entities.
1891	***Payne et al*** commented on the infectious nature of cutaneous warts and wart-like growths.
1896	***Jodassohn et al*** also made speculations and observations on the aetiology of warts and an infectious connection.
1901	***Heidingsfield et al*** studied and observed the findings in a prostitute, who complained of a condylomatous growth on her tongue after oral sexual activity; and suggesting a contagious mode of transmission of the etiologic infectious agent.

1907	***Ciuffo se al,*** performed experiments using the cellular filtrate of warts and transferring infectious growths. He concluded by suggesting a viral aetiology.
1911	***Francis Peyton Rous et al***, discovered the first oncogenic virus (RSV – Rous Sarcoma Virus).
1923	***Ullman et al*** postulated the aetiology of laryngeal papilloma with a virus.
1924	***Serra et al*** studied the occurrence of warts on genitals.
1933	Discovery of the Shope Virus/ Cottontail Rabbit Virus. ***Shope et al*** studied the growth and malignant transformation of cutaneous papilloma's in ten rabbits after inoculating them with a virus procured by him from 'cottontail' rabbits. The cancers developed in each one of the rabbits along with metastatic potentials and features in five out of the ten. This was the first investigation and proof that a virus could cause malignancy in mammals.
1949	***Strauss et al*** provided breakthrough evidence of viral particles presence in tissues procured from wart like growths. They observed intranuclear inclusion bodies in the epidermal cells of five cases of children with wart like lesions on their hands. On electron microscopic examination of the supernatant they observed spherical particles in a crystalline or layered arrangement; which was similar to the arrangement seen viral lesions.
1965	***Crawford et al*** and ***Klug & Finch et al*** studied the DNA structure of the 'Human Wart Virus', and found a circular double stranded DNA structure.
1967	***Rowson and Mahy et al*** termed the virus linked to viral growth as the 'Human Wart Virus'
1969	***Almeida et al*** performed particle agglutination studies and observed an antigenic difference in the cutaneous and genital wart viruses.

1972	It was popularly thought that the occurrence of cervical cancer was associated with the Herpes Simplex Virus (HSV), but after hybridization experiments the DNA isolated from cervical cancer tissues did not hybridize with HSV DNA strands; therefore, eliminating the involvement of HSV in cervical cancer.
1975	DNA sequencing technique emerges. ***Newell et al*** sees a dramatic increase (five to six-fold) in the occurrence of oral cancer in females with pre-existing cervical cancer. ***Zur et al*** was working with cancer causing Epstein-Barr Virus (EBV), and became interested in the fact that although cancer is not contagious how was it that cervical cancer was seemingly sexually transmitted, especially high rate of incidence in women who were young and sexually active and also with multiple sexual partners
1976	***Zur et al*** published an article "Condyloma Acuminata and Human Genital Cancer", in which he presented his hypothesis of HPV involvement in Cervical Cancer. ***Meisels*** and ***Fontin*** studied the cytologic features of cells isolated from the cervical cancer patients and noticed Koilocytic cells with a distinct halo. ***Gissmann L et al***, observed in their previous studies that different clinical pictures were observed via the viral agent, suggesting different subtypes and genetic heterogeneity in papilloma viruses which have a histologically similar picture.
1977	***Orth G et al***, reported the immunological, genetic and biochemical representation of another type of HPV isolated from warts commonly found on the hand. The restriction enzyme analysis revealed a different DNA in these lesions as compared to the DNA previously isolated from plantar warts. And no sequence

	homology was detected between the two DNAs. Further experimentation continued and by using molecular hybridization techniques they observed that the two viruses show diverse polypeptide patterns with dissimilar antigenic properties.
1982	The first Papillomavirus was sequenced. Namely the Bovine Papillomavirus 1 (BPV-1) by ***Chen et al***. The entire nucleotide sequence of the double-stranded circular DNA of BPV-1 was determined. Scrutiny of the findings in combination with other transcriptional data for the virus provided a basis for determining the organization of the papillomavirus genome.
1983	POLYMERASE CHAIN REACTION developed by ***Mullis et al.*** ***Zur et al*** performed experiments on the HPV strains isolated from cervical cancer samples and isolated HPV 6 and 11. He emphasised the strong link between HPV 6 and 11 in cervical cancer. ***Syrjanen et al*** gave the first hints of a possible association of HPV in Oral Squamous Cell Carcinoma. He performed experiments on oral premalignant lesions and demonstrated the presence of Papillomavirus in these lesions.
1984	HPV 18 was identified using human cell lines (HeLa lines) by ***Boskart et al.***
1985	Another batch of experiments by the same team on samples from German, Brazillian and African females led to the isolation of HPV 8,9,10 and 11. One HPV strain from a Brazilian patient did not match any of the existing strains and hence led to the discovery of HPV 18. HPV 16 was isolated by ***Gissman et al*** using the Southern Blot Hybridization technique with HPV 11. It was labelled as HPV 16 by ***Durst et al.***

	Simultaneously ***Schwartz et al*** were performing selective transcriptions of E6 and E7 genes, noticing specific deletions during the integration of viral DNA into host DNA. The findings of ***Schwarz et al*** were confirmed by ***Yee et al*** by further experiments. ***Loning et al*** and ***de Villiers*** also studied the presence of HPV in oral squamous cell carcinoma samples and suggested the presence of specific types in oral and oropharyngeal cancer. They tested 13 oral cancer samples out of which 3 tested positive for HPV 16, one tested positive for HPV 11 and one tested positive for HPV 27 (initially HPV 2)
1986	***Yasumoto et al*** researched the cellular transformation in rodent cells owing to viral oncogenes.
1987	***Durst et al*** and ***Pirisi et al*** observed cellular changes in keratinocytes by viral oncogenes.
1988	An evident association between high risk HPV and cervical cancer was made and established.
1990	***Werness et al*** investigated HPV 16, and observed the E6 protein binding to the p53.
1991	A recombinant L1 and L2 were assembled in vitro.
1992	***Dyson et al*** investigated HPV 16, and observed the E7 protein binding to pRb. The first phylogenetic tree of the human papillomavirus was suggested. Owing to global epidemiological studies (*Munoz and Bosch et al*), HPV 16 and 18 were recognised and major risk factors.

1993	Experimentation regarding the oncogenic potential of these viruses was underway. ***Lambert et al*** and ***Arbeit et al*** induced tumor growth in transgenic animals and observed the factors associated with it.
1995	The Organisation of IARC recognises HPV as potentially carcinogenic to humans. The first FDA approval for HPV DNA testing was approved.
1998	Monovalent HPV 16 vaccine trail
2000	Epidemiological studies confirm the involvement of HPV in Oropharyngeal carcinoma.
2002	Phase III 4v HPV vaccine trial
2003	Papillomaviridae was recognised as a distinct family.
2005	Phase III 2v HPV vaccine trail
2006	Quadrivalent Vaccine against HPV 6, 11, 18., licenced by FDA
2007	2v HPV licenced by Australia and EU
2009	2v HPV licensed by FDA; phase III 9v HPV vaccine trials
2014	WHO recommends a 2-dose schedule; 9v HPV FDA approval
2016	Data on 2-dose 9V HPV schedule in adolescents
2018	WHO prequalification of 9v HPV; Australia revised to 2-dose 9v HPV schedule
2020	A novel E. coli produced bivalent HPV vaccine licensed in China

HPV – Human Papillomavirus, FDA - U.S. Food and Drug Administration, IARC – International Agency FOR Research on Cancer, WHO – World Health Organisation, EU – European Union, E. coli – Escherichia coli

2.2 OROPHARYNGEAL CARCINOMA

Anatomically, the posterior part of the oral cavity comprises the pharynx, which is broadly divided into 3 compartments; nasopharynx, oropharynx and laryngopharynx (Figure 2.4).

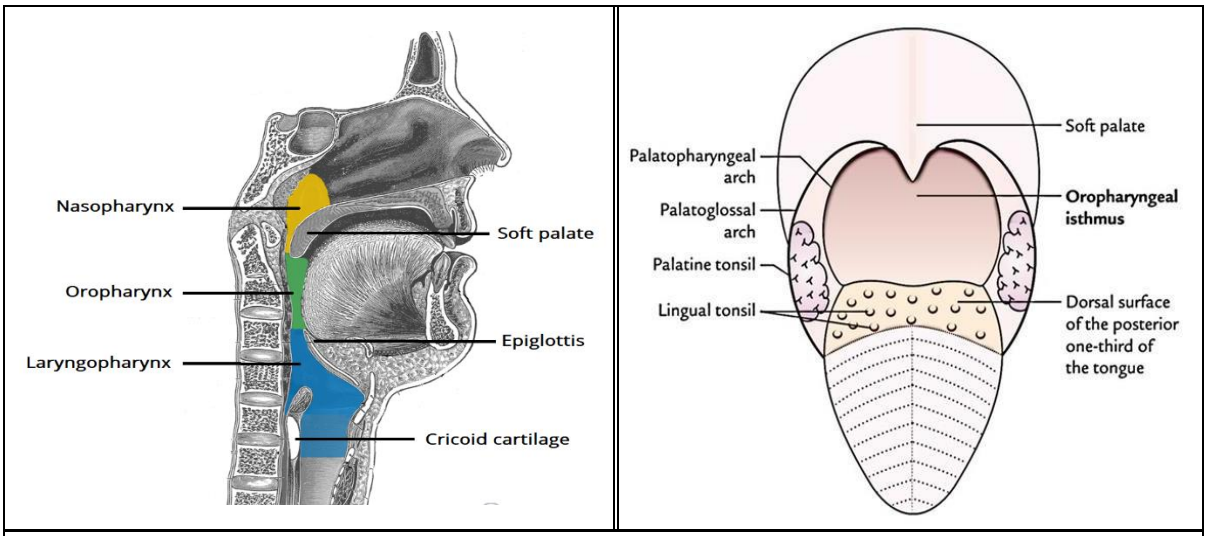


Figure 2.4: Parts of the throat / pharynx (left); anatomical boundaries of the oropharynx [60,61]

The contents of the oropharynx are base of the tongue, palatine tonsils, soft palate and oropharyngeal mucosa; anatomical boundaries of the oropharynx (Figure 2.4) are as follows:

- Anteriorly, circumvallate papillae of tongue and anterior tonsillar pillars
- Posteriorly, pharyngeal constrictor muscles
- Superiorly, soft palate
- Inferiorly, epiglottis and glossoepiglottic fold.

Head and neck cancer is the sixth most common cancer, with approximately 640,000 new cases each year worldwide[62]. Despite a general decline in the incidence of most head and neck cancers in recent years[63], the incidence of OPSCC has increased, especially in the developed world.

Approximately 90% of oropharyngeal cancers are squamous cell carcinomas[62]. The increase in incidence of OPSCC can be explained by the increase in HPV-related oropharyngeal carcinoma. For example, an advancing relative increase in the detection of HPV infection in OPSCC cases has been noted over the past three decades in Sweden (23.3% in 1970 to 93%

between 2006 and 2007)[64]. Similarly, HPV related OPSCC has been reported in 60-80% of the recent oropharyngeal cases in the US, compared with 40% in the prior decade[62].

HPV induced cancerous changes within cells are due to fluctuations in the genetic functioning of cells. This process has been well described in the flowchart below (Figure 2.5)

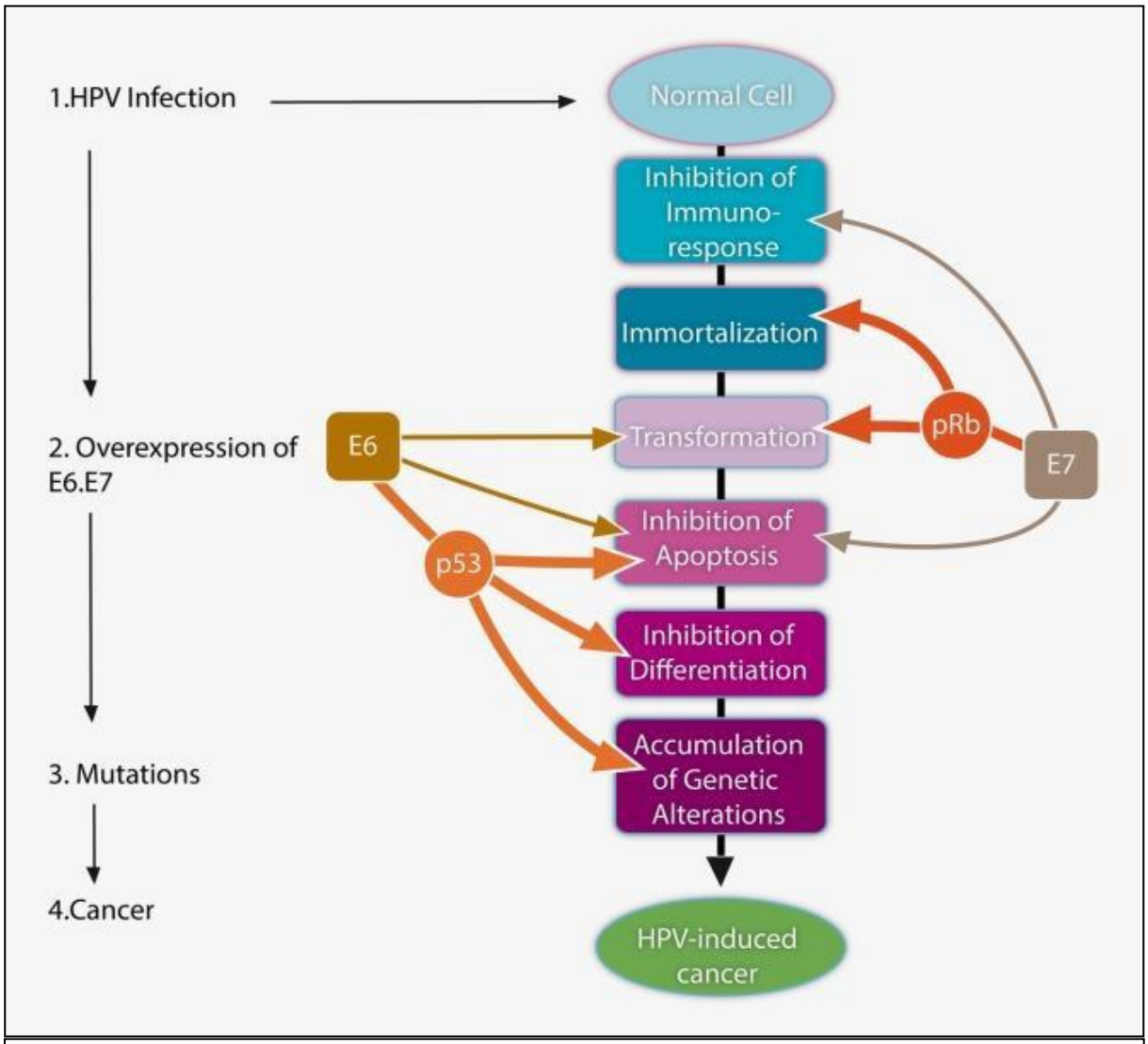


Figure 2.5: Simplified model illustrating viral oncogenes E6 and E7 which play a key role in the retraction of cell cycle control, apoptosis and promotion of genetic variability that contributes to the progress of cancer. [65]

HPV associated oropharyngeal carcinomas show distinct histological features including poor differentiation, scant keratinization and a basaloid phenotype (Figure 2.4).

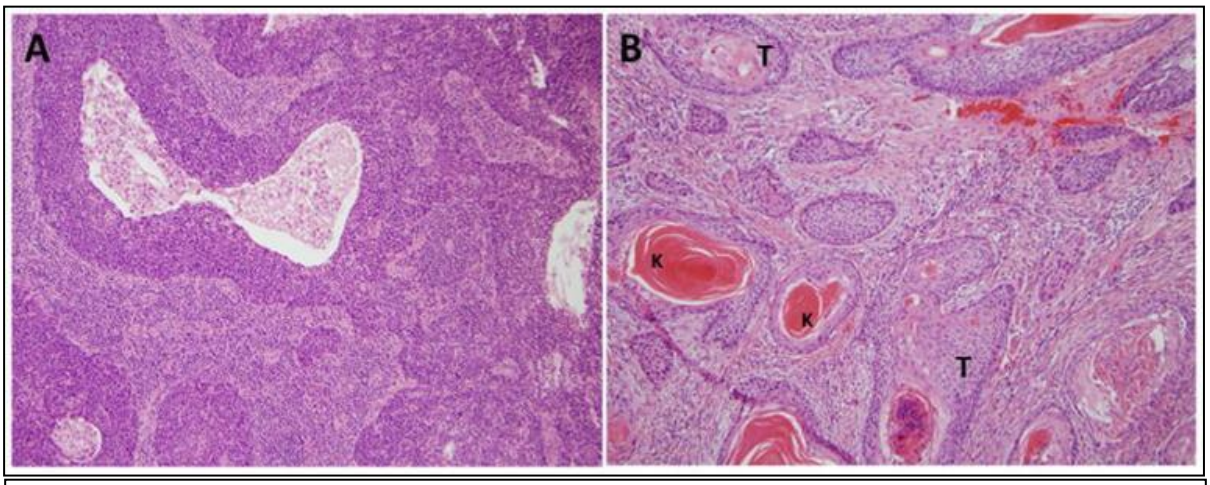


Figure 2.4: Distinct phenotypic features of HPV positive oropharyngeal carcinoma (A) as compared to HPV negative oropharyngeal carcinoma (B)[65]

Based on their association with cervical cancer and precursor lesions, HPVs can also be grouped to high- and low-risk HPV types. Low-risk HPV types include types 6, 11, 42, 43, and 44. High-risk HPV types include types 16, 18, 31, 33, 34, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, and 70. Included in the high-risk group are some HPV types that are less frequently found in cancers but are often found in squamous intraepithelial lesions (SILs)[66] (Table 2.4).

Table 2.4: HPV type and disease association[67]

Disease	HPV Type
Plantar warts	1, 2, 4, 63
Common warts	2, 1, 7, 4, 26, 27, 29, 41, 57, 65, 77, 1, 3, 4, 10, 28
Flat warts	3, 10, 26, 27, 28, 38, 41, 49, 75, 76
Other cutaneous lesions (e.g., epidermoid cysts, laryngeal carcinoma)	6, 11, 16, 30, 33, 36, 37, 38, 41, 48, 60, 72, 73
Epidermodysplasia verruciformis	2, 3, 10, 5, 8, 9, 12, 14, 15, 17, 19, 20, 21, 22, 23, 24, 25, 36, 37, 38, 47, 50
Recurrent respiratory papillomatosis	6, 11

Focal epithelial hyperplasia of Heck	13, 32
Conjunctival papilloma's/carcinomas	6, 11, 16
Condyloma acuminata (genital warts)	6, 11, 30, 42, 43, 45, 51, 54, 55, 70
Cervical intraepithelial neoplasia	
• **Unspecified**	30, 34, 39, 40, 53, 57, 59, 61, 62, 64, 66, 67, 68, 69
• **Low risk**	Low risk 6, 11, 16, 18, 31, 33, 35, 42, 43, 44, 45, 51, 52, 74
• **High risk**	16, 18, 6, 11, 31, 34, 33, 35, 39, 42, 44, 45, 51, 52, 56, 58, 66
Cervical carcinoma	16, 18, 31, 45, 33, 35, 39, 51, 52, 56, 58, 66, 68, 70

HPV related OPSCC has a more favourable prognosis than non-HPV related OPSCC, which has resulted in a scaling back of treatment intensity for these carcinomas[69,70]. The reason for an improved survival is partially understood; it may be the outcome of an amplified immunological response to HPV antigens in the host[71], or an augmented sensitivity to radiotherapy due to wild-type p53, causing an upsurge in apoptosis[72]. HPV status stratification for newly diagnosed patients is emphasised due to an improved prognosis.

The different methods to detect HPV status in a tumour specimen have been summarised below in Table 2.5.

Table 2.5: Methods of HPV detection[73]

Detection Method	Advantages	Disadvantages
PCR (Polymerase Chain Reaction)	High sensitivity	Low specificity
	Widely available	Cumbersome
DNA ISH (Deoxy ribonucleic Acid – In-situ Hybridization)	High specificity	Low sensitivity
E6/E7 mRNA (Messenger Ribonucleic Acid)	High sensitivity	May require fresh frozen tissue
	High specificity	Cumbersome
E6/E7 protein IHC (Immunohistochemistry)	High specificity	Questionable sensitivity
		Technically difficult
p16 IHC ((Immunohistochemistry)	Very high sensitivity	Questionable specificity
	Widely available	
Morphology	Always available	Imperfect correlation
	No expense	Questionable reproducibility

The burden of sexual transmission of HPV can be explained by the evolution of oral sexual behaviours leading to an increase in incidence of HPV related OPSCC[74,75]. Patients are typically younger[76], and as the consequences are comparatively favourable, there is an increased 5-year survival rate[75]. Other risk factors for OPSCC include tobacco consumption[77, 78], alcohol intake[78], poor dietary intake[76], superimposed bacterial or fungal infections (Candida)[79] and a range of sexual behaviours[75] (multiple sexual partners, unprotected sexual practices, early onset of sexual behaviours).

2.3 HPV VACCINE AND CANCER

HPV vaccine efficacy has been recorded as described below in Figure 2.7 by Zhou X et al[56] in 2020.

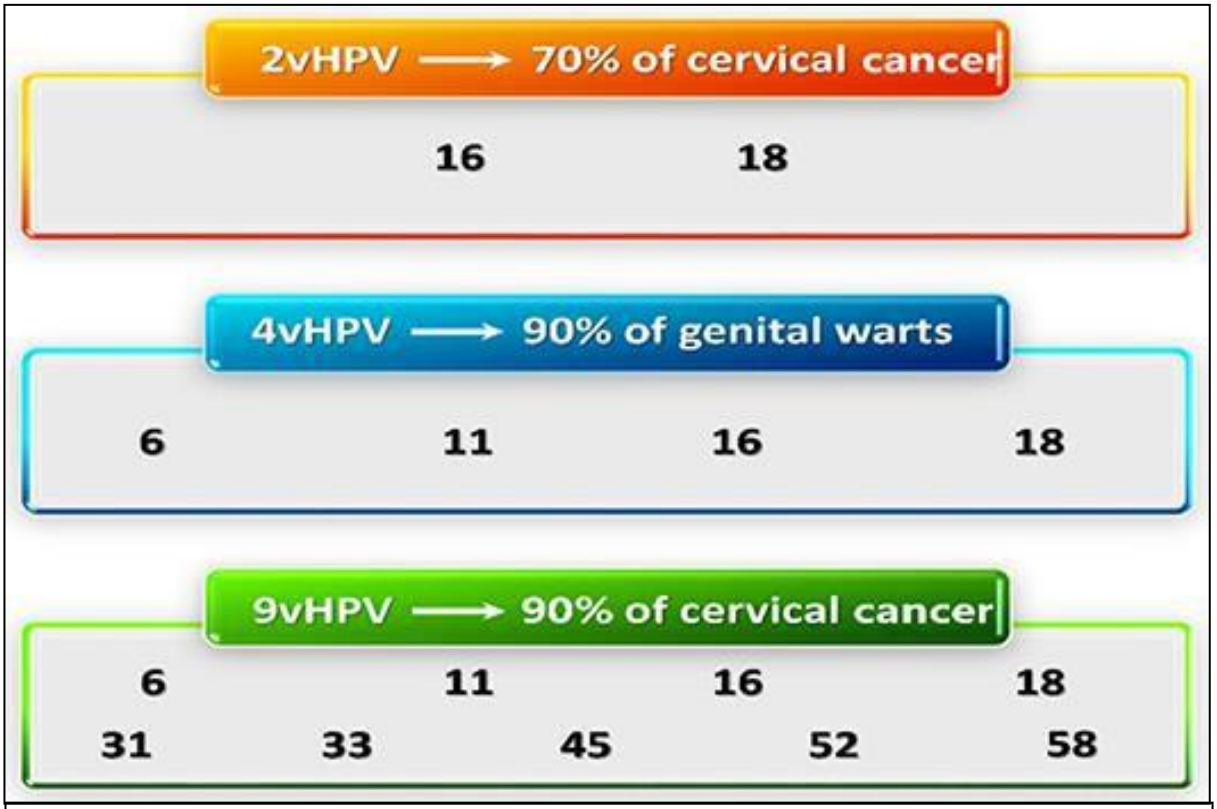


Figure 2.7 Vaccine efficacy[56]

As per a study in 2020, the coverage of prophylactic HPV vaccinations at a global level is slowest in Africa (1%) and Asia (2%).

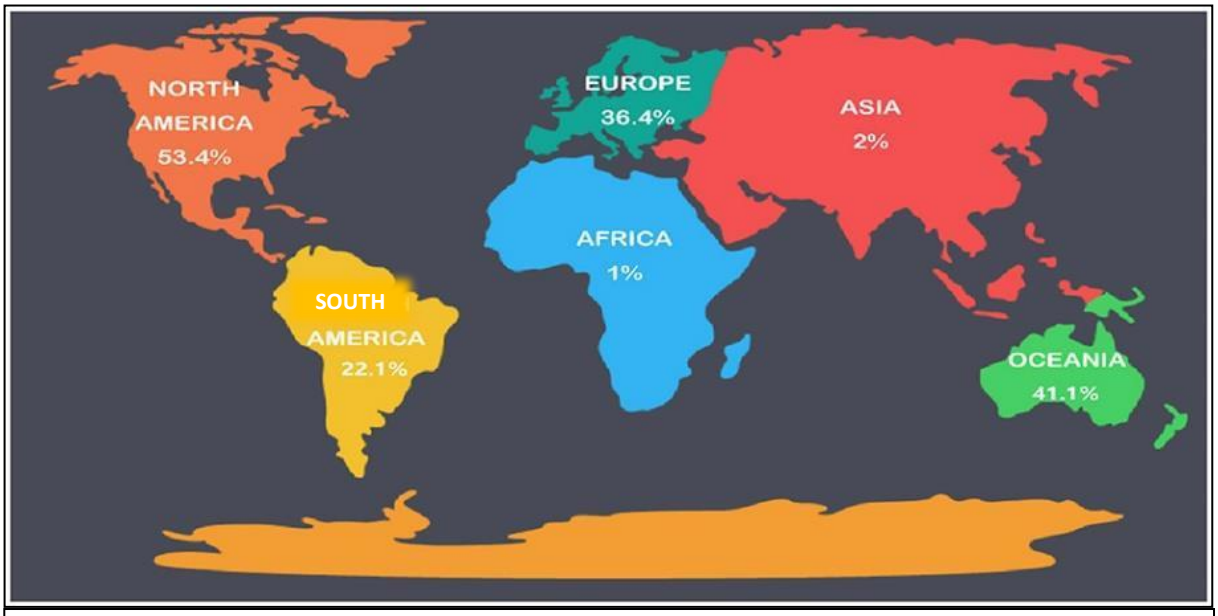


Figure 2.8 Progress of vaccination in prophylactic human papillomavirus vaccines[56]

Table 2.6 HPV vaccine timeline and chronological journey[57,58]

Year	Month	Agency	Vaccine	Recommendation/Approval
2006	June	FDA*	4v HPV	Approved vaccine for use in females 9-26 years of age
	June	ACIP	4v HPV	Recommended routine vaccine for females 11-12 years; catch-up 13-26 year; can be started at age 9
2009	October	FDA	2v HPV	Approved vaccine for females 10-25 years of age
	October	ACIP	2v HPV	Recommended vaccination for females 11-12 years, catch up 12-13 years; can be started at 9
	October	FDA	4v HPV	Approved vaccine for use males 9-26 years of age
	October	ACIP	4v HPV	Recommended vaccination may be given to males age 9-26 years – did not recommend routine vaccination
2011	October	ACIP	4v HPV	Recommended vaccination for males 11-12 years, catch up 13-21 years, and catch up 22-26 years for men who have sex with men or are immunocompromised; can be started at age 9.
2014	December	FDA	9v HPV	Approved use in females 9-26 years
			9v HPV	Approved use in males 9-15 years of age
2015	February	ACIP	9v HPV	Recommended routine vaccination for females 11-12 years; catch up 13-26 years; can be started at age 9
			9v HPV	Recommended routine vaccination for males 11-12 years; catch up 13-21 years; catch up 22-26 years

				for men who have sex with men or are immune compromised can be started at age 9
	December	FDA	9v HPV	Approved use in males 16-26 years of age
2016	October	FDA	9v HPV	Approved use of a two does option for males and females 9-14 years

*FDA – U.S. Food and Drug Administration, ACIP - Advisory Committee on Immunization Practices

2.4 INDIGENOUS PEOPLES

Indigenous peoples, as defined by the United Nations (2004)[80], includes all

'People with a historical continuity with pre-invasion and pre-colonial societies that developed on their territories, and who consider themselves distinct from other sectors of the societies now prevailing on those territories'.

Indigenous peoples are inheritors and practitioners of unique cultures and ways of relating to people and the environment. Indigenous peoples have retained social, cultural, economic and political characteristics that are distinct from those of the dominant societies in which they live. Indigenous peoples have sought recognition of personal identities, way of life, a right to traditional lands, territories and natural resources for centuries. Yet throughout history, rights have frequently been dishonoured and Indigenous peoples have been continually oppressed. There is now global recognition for the need of special measures which are necessary and required to protect the rights and culture of Indigenous peoples.[80]

Colonial settlements resulted in environmental dispossession of traditional lands and resources, which has negatively impacted Indigenous peoples' spiritual connections with the land and with each other.[81-84] Indigenous peoples are over-represented among the socially disadvantaged in almost every country, predominantly in developed countries.[85] Public policy created by colonial settlers in many countries has been aimed at the assimilation and cultural annihilation of Indigenous peoples, resulting in mass loss of culture, language and

community. Examples of assimilation policies include the Residential School System in Canada,[86] the Stolen Generations of Australia[87] and racial amalgamation in New Zealand.[88] Adelson's (2005)[89] notion of 'the embodiment of inequity', and similar works[80,81] have demanded attention be paid to the ways in which the impacts of colonial legacies, marginalisation and discrimination manifest in Indigenous peoples' health outcomes.[84] Previous works[85-88] have explored the relationship between colonisation and the intersectional nature of social determinants of health, such as race, demonstrating that healthcare patterns are rooted in historic economic, social and political circumstances and power relations.[89]

Globally, Indigenous peoples experience disproportionate health inequalities, in comparison to non-Indigenous populations, due to a unique history of colonial settlement.[90] Understanding the historical reasons for the ongoing health inequalities of Aboriginal and Torres Strait Islander health is critical in gaining the awareness to successfully engage with Aboriginal and Torres Strait Islander people and together envisaging a way forward. With the colonisation of Australia, the annihilation of the Aboriginal and Torres Strait Islander people began, through widespread massacres and the introduction of previously unknown infectious diseases. By 1850 only 10% of the Aboriginal and Torres Strait Islander population remained alive[91]. Aboriginal and Torres Strait Islander people were dispossessed of their lands and subsequently segregated onto reserves or missions. Government assimilation policies oversaw the widespread destruction of families and communities through the removal of their children, commonly referred to as the `stolen generations[92]. As Tom Calma, former Aboriginal Social Justice Commissioner stated; "Indigenous peoples are not merely `disadvantaged citizens´. The poverty and inequality that they experience is a contemporary reflection of their historical treatment as peoples. The inequality in health status that they continue to experience can be linked to systemic discrimination"[93].

Tom Calma went on to say that recognising the contemporary impact of colonisation on Aboriginal and Torres Strait Islander people remains a major challenge for those who seek to

understand the determinants of health among Aboriginal and Torres Strait Islander communities. Essentially, colonisation created significant barriers towards improving the health of Aboriginal and Torres Strait Islander people, and these barriers work on many levels; physician-patient interaction, delivery of health services as a whole, and the wider political and economic stage. Strategies and interventions need to be implemented at each of these levels to help create a holistic and culturally sensitive approach towards improving the health of Aboriginal and Torres Strait Islander people.

At the level of health care, it is necessary to broaden our definitions of health to include the physical, mental, and spiritual wellbeing of entire communities, not just the symptomatic treatment of the individual. Western biomedical models of health, with their predominant focus on diagnosis, treatment and prevention, have the effect of reducing the Aboriginal and Torres Strait Islander identity to a series of health problems that need fixing. The constant discourse over Aboriginal and Torres Strait Islander dysfunction and inadequacy in public health practice; "disconnects Aboriginal and Torres Strait Islander people from their own identities, in a manner similar to past oppressive policies of colonisation, assimilation and integration"[94]. Moreover, the dominance of the biomedical model has resulted in public health efforts predominately directed at addressing the lifestyle risk factors on a platform of "personal responsibility"; mainly through health education.

The Aboriginal and Torres Strait Islander construct of health is not just about the physical wellbeing of the individual. It is the social, emotional and cultural wellbeing of the entire community, a concept that is usually ignored by mainstream health services. It is therefore unsurprising that mainstream health services face additional challenges in trying to gain the trust of Aboriginal and Torres Strait Islander people. In terms of health service delivery, Aboriginal and Torres Strait Islander community controlled health services emphasise the importance of a holistic approach towards Aboriginal and Torres Strait Islander health care, where physical and mental wellbeing is linked to its historical and cultural context. They are also particularly vocal in deploring the lack of time spent on Aboriginal and Torres Strait

Islander studies in medical curriculums and are taking the initiative to educate non-Aboriginal and Torres Strait Islander doctors working with their organizations[95].

However, as Aboriginal and Torres Strait Islander Australians are a culturally, linguistically and experientially diverse population, national statistics may mask important geographic differences in their health and the determinants of their health. Cancer is a leading cause of mortality and reduced quality of life in the world, with a considerable and growing burden carried by low- and middle-income countries.

Indigenous peoples suffer from a disproportionate burden caused by increased rates of cancer detection and consequentially worse outcomes and prognosis.[96] Many factors contribute towards this inequality, including residing in remote locations, financial burdens, poor access to medical services, lack of awareness and mistrust in the medical system, compounded by implications of colonial legacies.[97]

There is limited research on the incidence of HPV infection and associated oropharyngeal cancer among the Indigenous populations of Australia. This is a considerable gap in the current information, particularly given the higher risk for oropharyngeal cancer among Indigenous populations. A more nuanced understanding of the risk factors associated with HPV infection and oropharyngeal carcinoma is necessary.

"To us, health is about so much more than simply not being sick. It's about getting a balance between physical, mental, emotional, cultural and spiritual health. Health and healing are interwoven, which means that one can't be separated from the other." – Aboriginal Medical Practitioner

2.5 REVIEW OF LITERATURE

The following section will combine the three key topics covered above, present a summary of the associated literature and identify research gaps. The first section will describe oral HPV infections amongst Indigenous populations at a global level. The second section will review the studies which have analysed the prevalence of oral HPV associated oropharyngeal carcinoma amongst Indigenous populations globally. The third section will reflect on findings specifically from Indigenous Australian data.

2.5.1 Oral HPV infection and Indigenous populations

More than 40 studies of the prevalence of cervical or genital HPV infection in Indigenous populations at a global level have been reported. Only one study, Garza-Ramos et al[97] in 2020, reported the prevalence of oral HPV infection in an Indigenous community (Mexico). The authors observed an oral HPV infection prevalence of 12.1%, with most observed HPV types associated with benign pathologies. The authors reported a significant association between oral HPV infection and different sexual behaviours, such as multiple partners, unsafe sexual and oral sexual practices (i.e. without condoms or dental dams). The most prominent HPV type was HPV 13, which is associated with Heck's disease (also known as Focal Epithelial Hyperplasia, it is an asymptomatic, benign neoplastic condition characterized by multiple white to pinkish papules that occur diffusely in the oral cavity, associated with HPV 13 or 32). There were no adverse consequences reported.

2.5.2 Oropharyngeal carcinoma and Indigenous populations

Five studies[98-102] have reported the prevalence of oropharyngeal carcinoma in Indigenous population groups. None have investigated oral HPV infection associated oropharyngeal carcinoma among the population groups. Two studies reported differences between Indigenous and non-Indigenous population groups of different regions in Canada.

Kelly et al[98] found Alaska Indian men compared with New Mexico Indian men had increased prevalence of oral cavity/pharynx (specifically nasopharynx) cancers. They found that, in comparison with U.S. Whites, Alaska Indians had a higher overall rate of oral cavity/pharynx cancers. The incidence rates for nasopharyngeal and gallbladder cancer among Alaska Indian men was more than 10 times the U.S. Whites.

Carriere et al[99] reported the prevalence of cancers on the basis of oral cavity site affected in Canada, comparing both Indigenous (Inuit Nunangat) and non-Indigenous populations. The authors found that rates were higher among the Inuit Nunangat population compared with other Canadians. Particularly, the rate of cancer of the buccal cavity and pharynx was reported to be more than 4 times higher among females in Inuit Nunangat than among females in the rest of Canada.

Frydrych AM et al[100] explored the prevalence of oral and oropharyngeal carcinoma in an Indigenous population of Western Australia. The population sample was small (n=*), and there were no differences noted in the prevalence of oropharyngeal carcinoma among Aboriginal and non-Aboriginal population groups.

Chelimo et al[101] investigated the incidence of oropharyngeal and oral cavity squamous cell cancers by subsite, age, gender, ethnicity and social deprivation in New Zealand. The authors reported that Māori (New Zealand Indigenous population) had higher oropharyngeal cancer rates but lower oral cavity cancer rates than European/other ethnicities. This was the only study that mentioned the association of oral HPV infection and cancer of the oral cavity. The positive

impact of future vaccinations on the increasing rates of HPV associated carcinomas was described.

Erickson B et al[102] performed a study to determine whether there is a difference in epidemiology and survival outcomes between First Nations (Indigenous population groups of Canada) and non-First Nations patients with oral cancers. The authors found that although the mean incidence from 1998–2009 was not significantly different between First Nations and non-First Nations patients, disease specific survival was lower among Indigenous patients, with a 5-year rate of 44.5% compared to 67.8% for non-Indigenous patients.

2.5.3 HPV associated oropharyngeal carcinoma in Indigenous Australians

The Cancer data registry[103] of Australia reports the overrepresentation of Indigenous Australians in almost all cancer statistics, including cancers of the head and neck. Analysing the incidence trends for head and neck cancer from 2009 to 2013 shows that Indigenous Australians are 1.9 times more likely to be diagnosed than non–Indigenous Australians, and are 3.4 times more likely to succumb to the diagnosis.[104] Risk of cancer death was associated with advanced stage at first observation, with more Indigenous than non-Indigenous individuals having distant metastases at diagnosis.

Although there have been reports[105] of a dramatic increase of HPV infection from 1987-2010 (20.2%-63.5%), there have been no studies or reports which have specifically indicated the prevalence of oral HPV infection in Indigenous population groups of Australia. It is hypothesized that the prevalence of this infection would be high, given the HPV vaccine course completion rates across Indigenous adolescents is low.[106]

2.6 THESIS AIM

As the above literature suggests there is a particular dearth of information available on the prevalence HPV infection and its associated oropharyngeal carcinoma amongst Indigenous

populations. The aim of this study was to address this gap and to evaluate the burden of HPV infection and its associated cancers amongst Indigenous populations of South Australia. The experiences and barriers faced by Indigenous populations in regards to HPV infection, HPV vaccinations and OPSCC at a global level will be additionally be analysed.

The format of this thesis is by publication. To aid the reader, clear navigation links have been included across sections and Chapters. Each section begins with an overview that outlines the Chapters in that respective section and ends with a section summary. Similarly, each Chapter begins with a preface.

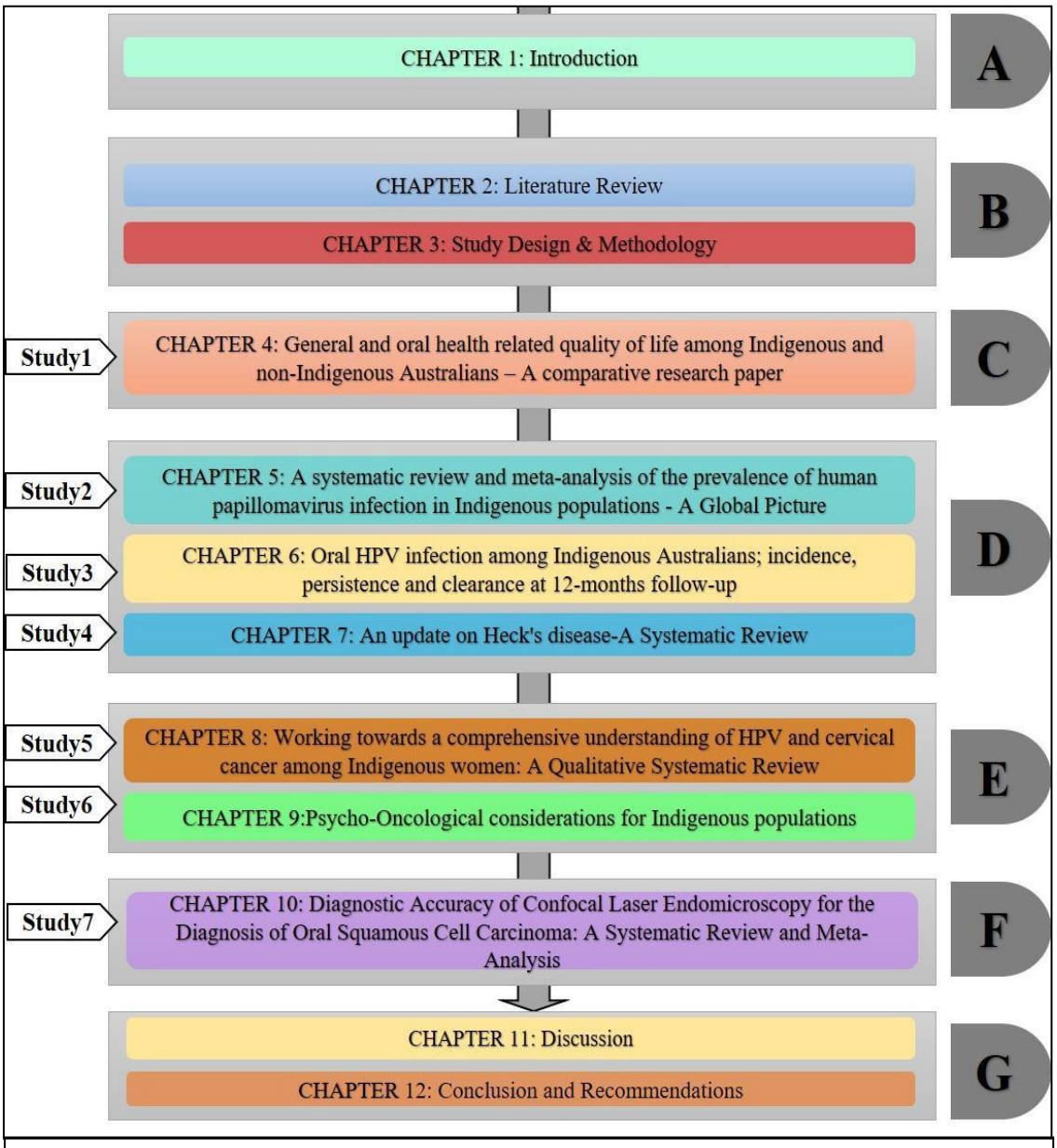


Figure 2.9: Flowchart illustrating the thesis structure

2.7. References:

1. Doorbar J, Egawa N, Griffin H, Kranjec C, Murakami I. Human papillomavirus molecular biology and disease association. Rev Med Virol. 2015;25 Suppl 1(Suppl 1):2–23. doi:10.1002/rmv.1822
2. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Human Papillomaviruses. Lyon (FR): International Agency for Research on Cancer; 2007. (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, No. 90.) 1, Human Papillomavirus (HPV) Infection. Available from: https://www.ncbi.nlm.nih.gov/books/NBK321770
3. Stanley MA. Epithelial cell responses to infection with human papillomavirus. Clin Microbiol Rev. 2012 Apr;25(2):215-22. doi: 10.1128/CMR.05028-11. PMID: 22491770; PMCID: PMC3346303.
4. McMurray HR, Nguyen D, Westbrook TF, McAnce DJ. Biology of human papillomaviruses. Int J Exp Pathol. 2001;82(1):15-33. doi:10.1046/j.1365-2613.2001.00177.x
5. Harden ME, Munger K. Human papillomavirus molecular biology. Mutat Res Rev Mutat Res. 2017; 772:3–12. doi: 10.1016/j.mrrev.2016.07.002
6. Syrjanen, S. and K. Syrjanen (2008). "The history of papillomavirus research." Cent Eur J Public Health 16 Suppl: S7-13.
7. Gross L. Papilloma's, warts, and related neoplasms in rabbits, dogs, horses, cattle, hamsters and in man. Oncogenic Viruses. Volume 2. 3rd ed. Oxford: Pergamon Press; 1983.
8. Orth G. Epidermodysplasia verruciformis: a model for understanding the oncogenicity of human papillomaviruses. Ciba Found Symp. 1986;120: l57-74.

9. Oriel JD. Pathogenesis. In: Von Krogh G, Rylander E, editors. GPVI. Genito anal papillomavirus infection: a survey for the clinician. Karlstad: ConpharmAB; 1989
10. Zur Hausen H, de Villiers EM. Human papillomaviruses. Ann Rev Microbial. 1994; 48:427-47.
11. Lowy DR. History of papillomavirus research. In: Campo MS, editor. Papillomavirus research: from natural history to vaccines and beyond. Hethersett: Caister Academic Press; 2006. p. 13-28.
12. Rigoni-Stem A. Statistics relating to cancerous diseases. Gior Serviré Progr Pathol Terap. 1842; 2:507-17.
13. Payne J. On the contagious rise of common warts. Br J Dermatol. 1891; 3:185.
14. Adassohn J. Are common warts contagious? Verhandel D Deutsch Dem Gesellseh. 1896; 5:497-512.
15. Heidingsfreld ML. Flat acuminate warts. J Cutan Genitourinary Dis. 1901; 19:226-34
16. Ciuffo G. Positive transfer with a filtrate of the common wart. Gior Ital D Mai Ven.1907; 48:12-7.
17. Serra A. Studies on the virus of warts, papilloma and acuminata warts. Giomale Italiano delle Malattie Veneree e delle Pelle. 1924; 65:1808-14. (In Italian.)
18. Ullman EV. On the aetiology of the laryngeal papilloma. Aeta Otolaryngol. 1923; 5:317-34.
19. Findlay GM. Warts. In: A system of bacteriology in relation to medicine. Volume 7, Chapter XVIII. London: Great Britain Medical Research Council;1930. p. 252-258.
20. Strauss MJ, Shaw EW, Bunting HL, Melnick J. Crystalline virus-like particles from skin papilloma's characterized by intranuclear inclusion bodies. Proc Soe Exp Biol Med. 1949 Oct;72(l):46-50.

21. Shope RE, Hurst EW. Infectious papillomatosis of rabbits: with a note on the histopathology. J Exp Med. 1933; 58:607-24.
22. Rous P, Beard JW. The progression to carcinoma of virus-induced rabbit papilloma's (Shope). J Exp Med. 1935; 62:523-48.
23. Rous P, Kidd JG. The carcinogenic effect of a papilloma virus on the tarred skin of rabbits. I. Description of the phenomenon. J Exp Med. 1938; 67:399-422.
24. Rous P, Friedewald WF. The effect of chemical carcinogens on virus induced rabbit papilloma's. J Exp Med. l944; 79:511-38.
25. Syverton JT, Daseomb HE, Wells EB, Koomen J Jr, Berry GP. The virus induced rabbit papilloma-to-carcinoma sequence. II. Carcinomas in the natural host, the cottontail rabbit. Cancer Res. 1950 Jul; IO (7):44O-4.
26. Parsons RJ, Kidd JG. Oral papillomatosis of rabbis: a virus disease. J Exp Med. 1943; 77:233-50.
27. Olson C Jr, Cook RH. Cutaneous sarcoma-like lesions of the horse caused by the agent of bovine papilloma. Proc Soe Exp Biol Med. 1951 Jun;77(2):28l-4.
28. Barrett TJ, Silbar JD, McGinley JP. Genital warts- a venereal disease. J Am Med Assoc. 1954 Jan 23;154(4):333-4.
29. Ayre JE, Ayre WB. Progression of pre-cancer stage to early carcinoma of cervix within one year; combined cytologic and histologic study with report of a case. Am J Clin Pathol. 1949 Aug;19(8):770-8.
30. Koss LG, Durfee GR. Unusual patterns of squamous epithelium of the uterine cervix: cytologic and pathologic study of koilocytotic atypia. Ann NY Acad Sei. 1956 Mar 30;63(6): 1245-61.

31. Koss LG. Carcinogenesis in the uterine cervix and Human papillomavirus infection. In: Syrjanen K, Gissmann L, Koss LG, editors. Papillomaviruses and human disease. Heidelberg: Springer-Verlag; 1987. p. 235-67.
32. Lewandowski T, Lutz W. An ease of a hitherto undescribed skin disease (Epidermodysplasia verruciformis). Arch Dermatol Syphilol. 1922; 141:193.
33. Jablonska S, Milewski B. Information on epidermodysplasia verruciformis Lewandowsky-Lutz; positive results of auto- and heteroinoeulation. Dermatological. 1957Jul;115(1):1-22.
34. Ito Y, Evans CA. Induction of tumours in domestic rabbits with nucleic acid preparations from partially purified Shope papilloma virus and from extracts of papillomata of domestic and cottontail rabbits. J Exp Med. 1961 ¡114:485-500.
35. Crawford LV. A study of human papilloma virus DNA. J Mol Biol. 1965 Sep;13(2):362-72.
36. Klug A, Finch JT. Structure of viruses of the papilloma polyoma type. I. Human wart virus. J Mol Biol. 1965 Feb; 11:403-23.
37. Dunn AE, Ogilvie MM. Intranuclear virus particles in human genital wart tissue observations on the ultrastructure of the epidermal layer. J Ultrastr Res. 1968Feb;22(3):282-95.
38. Almeida JD, Oriel JD, Stannard LM. Characterization of the virus found in human genital warts. Microbios. 1969; 3:225-32.
39. Melnick JL. Papova virus group. Science. 1962 Mar 3O; I35:1128-30.
40. Rowson KE, Mahy BW. Human papova (wart) virus. Bacteriol Rev. 1967 Jun;3l (2):110-31.
41. Pyrhönen S, Penttinen K. Wart-virus antibodies and the prognosis of wart disease. Lancet. 1972 Dee 23;2(7791):1330-2.

42. Pyrhönen S, Johansson E. Regression of warts. An immunological study. Lancet. 1975 Mar 15; l (7907):592-6.
43. Pyrhönen S, Neuvonen E. The occurrence of human wart-virus antibodies in dogs, pigs, and cattle. Arch Virol. 1978;57(4):297-305.
44. Pyrhönen S. Human wart-virus antibodies in patients with genital and skin warts. Acta Derm Venereal. 1978;58(5):427-32..
45. Zur Hausen H, Meinhof W, Scheiber W, Bomkamm GW. Attempts to detect virus specific DNA in human tumours. I. Nucleic acid hybridizations with complementary RNA of human wart virus. Int J Cancer. 1974 May 15;13(5):650-6.
46. Zur Hausen H, Gissmann L, Steiner W, Dippold W, Dreger I. Human papilloma viruses and cancer. BibI Haematol. 1975 Oct;(43):569-71.
47. Zur Hausen H. Condylomata acuminata and human genital cancer. Cancer Res. 1976Feb;36(2pt2):794.
48. Gissmann L, Zur Hausen HZ. Human papilloma virus DNA: physical mapping and genetic heterogeneity. Proc Nati Acad Sei USA. 1976 Apr;73(4):1310-3.
49. Gissmann L, Pfister H, Zur Hausen H. Human papilloma viruses (HPV): characterization of four different isolates. Virology. 1977 Feb;76(2): 569-80.
50. Orth G, Favre M, Croissant O. Characterization of a new type of human papillomavirus that causes skin warts. J Virol. 1977 Oct;24(l): 108-20.
51. Pfister H, Zur Hausen H. Sero-epidemiological studies of human papilloma virus (HPV 1) infections. Int J Cancer. 1978 Feb 15;21(2):16l-65.
52. Meisels A, Fortin R. Condylomatous lesions of the cervix and vagina. I. Cytologic patterns. Acta Cytol. 1976 Nov-Dec;20(6):505-9.
53. Purola E, Savia E. Cytology of gynaecologic condyloma acuminatum. Acta Cytol. 1977 Jan-Feb;21 (1):26-31

54. Delia Torre G, Pilotti S, de Palo G, Rilke F. Viral particles in cervical condylomatous lesions. Tumori. 1978 Oct 31 ;64(5):549-53.
55. Hills E, Laverty CR. Electron microscope detection of papilloma virus particles in selected koilocytotic cells in a routine cervical smear. Acta Cytol. 1979Jan-Feb;23(l):53-6
56. Zhou X, Sun L, Yao X, Li G, Wang Y and Lin Y. Progress in vaccination of prophylactic human papillomavirus vaccine. Front Immunol 2020; 11:1434 DOI=10.3389/fimmu.2020.01434
57. Schiller, J., Davies, P. Delivering on the promise: HPV vaccines and cervical cancer. Nat Rev Microbiol 2, 343–347 (2004). https://doi.org/10.1038/nrmicro867
58. Daley, Ellen & Vamos, Cheryl & Thompson, Erika & Zimet, Gregory & Rosberger, Zeev & Merrell, Laura & Kline, Nolan. (2017). The Feminization of HPV: How Science, Politics, Economics and Gender Norms Shaped U.S. HPV Vaccine Implementation. Papillomavirus Research. 3. 10.1016/j.pvr.2017.04.004.
59. Pan C, Issaeva N, Yarbrough WG. HPV-driven oropharyngeal cancer: current knowledge of molecular biology and mechanisms of carcinogenesis. Cancers Head Neck. 2018; 3:12. Published 2018 Dec 29. doi:10.1186/s41199-018-0039-3
60. https://www.earthslab.com/anatomy/oropharynx/
61. Pazhaniappan N. https://teachmeanatomy.info/neck/viscera/pharynx/ 2019
62. National Cancer Institute. Surveillance epidemiology and end results. 2019 http://seer.cancer.gov/faststats/selections.php#Output.
63. Ariyawardana A, Johnson NW. Trends of lip, oral cavity and oropharyngeal cancers in Australia 1982-2008: overall good news but with rising rates in the oropharynx. BMC Cancer 2013 Jul 06; 13:333

64. Nasman A, Attner P, Hammarstedt L, Du J, Eriksson M, Giraud G, et al. Incidence of human papillomavirus (HPV) positive tonsillar carcinoma in Stockholm, Sweden: an epidemic of viral-induced carcinoma? Int J Cancer2009; 125:362-6.
65. Liu C, Mann D, Sinha UK, Kokot NC. The molecular mechanisms of increased radiosensitivity of HPV-positive oropharyngeal squamous cell carcinoma (OPSCC): an extensive review. J Otolaryngol Head Neck Surg. 2018 Sep 21;47(1):59. doi: 10.1186/s40463-018-0302-y. PMID: 30241572; PMCID: PMC6150985.
66. Miller DL, Puricelli MD, Stack MS. Virology and molecular pathogenesis of HPV (human papillomavirus)-associated oropharyngeal squamous cell carcinoma. Biochem J. 2012;443(2):339-353. doi:10.1042/BJ20112017
67. Burd EM. Human papillomavirus and cervical cancer. Clin Microbiol Rev. 2003;16(1):1-17. doi:10.1128/CMR.16.1.1-17.2003.
68. Mirghani H, Amen F, Blanchard P, Moreau F, Guigay J, Hartl DM, Lacau St Guily J. Treatment de-escalation in HPV-positive oropharyngeal carcinoma: ongoing trials, critical issues and perspectives. Int J Cancer. 2015 Apr 1;136(7):1494-503. doi: 10.1002/ijc.28847. Epub 2014 Apr 4. PMID: 24622970.
69. Strohl MP, Wai KC, Ha PK. De-intensification strategies in HPV-related oropharyngeal squamous cell carcinoma-a narrative review. Ann Transl Med. 2020;8(23):1601. doi:10.21037/atm-20-2984.
70. Dahlstrand H, Dahlgren L, Lindquist D, Munck-Wikland E, Dalianis T. Presence of human papillomavirus in tonsillar cancer is a favourable prognostic factor for clinical outcome. Anticancer Res2004; 24:1829-35.
71. Lindel K, Beer KT, Laissue J, Greiner RH, Aebersold DM. Human papillomavirus positive squamous cell carcinoma of the oropharynx. A radiosensitive subgroup of head and neck carcinoma. Cancer 2001; 92:805-13.

72. Liu, C., Mann, D., Sinha, U.K. et al. The molecular mechanisms of increased radio sensitivity of HPV-positive oropharyngeal squamous cell carcinoma (OPSCC): an extensive review. J of Otolaryngol - Head & Neck Surg 47, 59 (2018). https://doi.org/10.1186/s40463-018-0302-y
73. Allen CT, Lewis JS Jr, El-Mofty SK, Haughey BH, Nussenbaum B. Human papillomavirus and oropharynx cancer: biology, detection and clinical implications. Laryngoscope. 2010 Sep;120(9):1756-72. doi: 10.1002/lary.20936. PMID: 20669304.
74. Worden FP, Hooton J, Lee J, Eisbruch A, Wolf GT, Prince M, et al. Association of tobacco (T) use with risk of distant metastases (DM), tumor recurrence, and death in patients (pts) with HPV-positive (+) squamous cell cancer of the oropharynx (SCCOP). J Clin Oncol 2009; 27:15s.
75. Heck JE, Berthiller J, Vaccarella S, Winn DM, Smith EM, et al. Sexual behaviours and the risk of head and neck cancers: a pooled analysis in the International Head and Neck Cancer Epidemiology (INHANCE) consortium. Int J Epidemiol 2009; Published online 18 December.
76. Majchrzak E, Szybiak B, Wegner A, et al. Oral cavity and oropharyngeal squamous cell carcinoma in young adults: a review of the literature. Radiol Oncol. 2014;48(1):1- 10. Published 2014 Jan 22. doi:10.2478/raon-2013-0057.
77. Radoï L, Luce D. A review of risk factors for oral cavity cancer: the importance of a standardized case definition. Community Dent Oral Epidemiol 2013 Apr;41(2):97-109.
78. Friborg JT, Yuan JM, Wang R, Koh WP, Lee HP, Yu MC. A prospective study of tobacco and alcohol use as risk factors for pharyngeal carcinomas in Singapore Chinese. Cancer 2007 Mar 15;109(6):1183-1191

79. Perera M, Al-Hebshi NN, Perera I, Ipe D, Ulett GC, Speicher DJ, et al. A dysbiotic mycobiome dominated by Candida Albicans is identified within oral squamous-cell carcinomas. J Oral Microbiol 2017 Oct;9(1):1385369
80. United Nations (2004) https ://www.un.org/development /desa/indigenous peoples/ declaration-on-the-rights-of-indigenous-peoples.html
81. Axelsson P, Kukutai T, Kippen R. The field of Indigenous health and the role of colonisation and history. J Popul Res 2016; 33:1–7.doi:10.1007/s12546-016-9163-2
82. Paradies Y. Colonisation, racism and Indigenous health. J Popul Res 2016; 33:83–96.doi:10.1007/s12546-016-9159-y
83. Richmond CAM, Ross NA. The determinants of first nation and Inuit health: a critical population health approach. Health Place 2009; 15:403–11
84. Valeggia CR, Snodgrass JJ. Health of Indigenous peoples. Annual Rev Anthropol 2015; 44:117–35.doi:10.1146/annurev-anthro-102214-013831
85. Gracey M, King M. Indigenous health part 1: determinants and disease patterns. Lancet 2009; 374:65–75.doi:10.1016/S0140-6736(09)60914-4
86. Bombay A, Matheson K, Anisman H. The intergenerational effects of Indian residential schools: implications for the concept of historical trauma. Trans Cult Psychiatry 2014; 51:320–38.doi:10.1177/1363461513503380
87. Rigney LI. Native title, the stolen generation and reconciliation. Interventions 1998; 1:125–30.doi:10.1080/13698019800510181
88. Williams DV. The continuing impact of amalgamation, assimilation and integration policies. J R Soc N Z 2019; 49:34–47.doi:10.1080/03036758.2019.1677252
89. Adelson N. The embodiment of inequity: health disparities in Aboriginal Canada. Can J Public Health 2005;96 Suppl 2: S45–61.doi:10.1007/BF03403702pmid: http ://www. ncbi. nlm.nih.gov/pubmed/16078555

90. Sa T, JP, KP. Assimilation and acculturation in native Hawaiian and other Pacific Islander (NHOPI) health and well-being. POJ Nurs Prac Res 2020; 4:1–5.doi:10.32648/2577-9516/4/1/1
91. Purdie N, Dudgeon P, Walker R: Working Together: Aboriginal and Torres Strait Islander Mental Health and Wellbeing Principles and Practice. 2010, Department of Health and Ageing, Canberra
92. Social determinants and the health of indigenous peoples in Australia - a human rights based approach.., [https://www.humanrights.gov.au/news/speeches/social-determinants-and-health-indigenous-peoples-australia-human-rights-based]
93. Henry BR, Houston S, Mooney GH: Institutional racism in Australian healthcare: a plea for decency. Med J Aust. 2004, 180: 517-520.
94. Australian Bureau of Statistics (ABS): 2076.0 - Census of population and housing: characteristics of Aboriginal and Torres Strait Islander Australians. first issue.2011.
95. Allan B, Smylie J. First peoples, second class treatment: the role of racism in the health and well-being of Indigenous peoples in Canada. Toronto: Wellesley Institute, 2015.
96. Bourassa C, McKay-McNabb K. Racism, Sexism and Colonialism: The Impact on the Health of Aboriginal Women In: Canadian woman studies: an introductory reader. Toronto: Inanna Publications, 2006: 540–51.
97. de la Garza-Ramos MA, Urrutia-Baca VH, Urbina-Rios CS, García-Robayo DA, Tamez-Guerra P, Gomez-Flores R. Prevalence of human papillomavirus in the oral cavity of an indigenous community from Southwest México. Infect Genet Evol. 2020 Sep; 83:104283. doi: 10.1016/j.meegid.2020.104283. Epub 2020 Mar 17. PMID: 32194258.

98. Kelly JJ, Lanier AP, Alberts A and Wiggins CL. Differences in cancer Incidence among Indians in Alaska and New Mexico and US whites, 1993-2002. Can Epidemiol Biomarkers and Prev 2006. DOI: 10.1158/1055-9965.EPI-05-0454

99. Carrière GM, Tjepkema M, Pennock J, Goedhuis N. Cancer patterns in Inuit Nunangat: 1998-2007. Int J Circumpolar Health. 2012 May 15; 71:18581. doi: 10.3402/ijch. v71i0.18581. PMID: 22663938; PMCID: PMC3417551.

100. Frydrych AM, Slack-Smith LM, Parsons R, Threlfall T. Oral cavity squamous cell carcinoma—characteristics and survival in aboriginal and non-aboriginal Western Australians. Open Dent J. 2014; 8:168-174.

101. Chelimo C, Elwood JM. Sociodemographic differences in the incidence of oropharyngeal and oral cavity squamous cell cancers in New Zealand. Aust N Z J Public Health. 2015; 39:162-167.

102. Erickson B, Biron VL, Zhang H, Seikaly H, Côté DW. Survival outcomes of First Nations patients with oral cavity squamous cell carcinoma (Poliquin 2014). J Otolaryngol Head Neck Surg. 2015;44(1):4. Published 2015 Feb 3. doi:10.1186/s40463-015-0056-8.

103. Cancer Australia. Aboriginal and Torres Strait Islander Cancer Statistics. Australian Government; 2018.

104. Australian Institute of Health and Welfare. Cancer in Aboriginal and Torres Strait Islander people of Australia. Australian Institute of Health and Welfare; 2018.

105. Hong A, Lee CS, Jones D, Veillard AS, Zhang M, Zhang X, et al. Rising prevalence of human papillomavirus-related oropharyngeal cancer in Australia over the last 2 decades. Head Neck 2016 May;38(5):743-750.

106. Brotherton JM, Winch KL, Chappell G, et al. HPV vaccination coverage and course completion rates for Indigenous Australian adolescents, 2015. Med J Aust. 2019;211(1):31-36. doi:10.5694/mja2.5022

SECTION B:

METHODOLOGY AND STUDY DESIGN

Overview of Section B

Section B of the thesis comprises Chapter 3, which provides the basis, background, and design for the research conducted.

Chapter 3 presents the aims and objectives, research questions, and conceptual framework of the study. A broad outline of the study design, description of the data sources used, and the overall methodological framework and analytical approach used in this research is also provided.

03

Study Design and Methodology

3.1 PREFACE

In this Chapter, a brief background to the research project is provided in Section 3.2 followed by the overall aims and specific objectives of this thesis in Section 3.3. The research questions used to address these aims and objectives are listed in Section 3.4, followed by the description of the overall study setting, design and period in Section 3.5.

Although efforts have been made to minimise repetition between the details provided in this Chapter and those outlined in each manuscript, some may still exist.

3.2 BACKGROUND TO THIS RESEARCH

The research conducted in this thesis was part of a national project 'Human Papillomavirus and Oropharyngeal Cancer Among Indigenous Australians' (HPV-OPC) funded by the National Health and Medical Research Council (NHMRC). Led by the University of Adelaide, the project also involved researchers from the Menzies School of Health Research (Darwin), Aboriginal Health Council of South Australia (Adelaide), Yaitya Purruna Indigenous Health Unit (Adelaide), Aboriginal Health Division Women's and Children's Health Network (Adelaide), Pika Wiya Health Service Inc. (Port Augusta), Wardliparingga Aboriginal Research Unit, South Australian Health & Medical Research Institute (Adelaide), School of Health Sciences (University of South Australia, Adelaide), Griffith University (Gold Coast), Cancer Council of New South Wales (Sydney) and QIMR Berghofer Medical Research Institute (Brisbane).

The aims of the HPV-OPC study were as follows:

1. To yield population estimates of the age-specific prevalence of oncogenic genotypes of HPV in the mouth and oropharynx of defined Aboriginal and Torres Strait Islander populations (male and female).

   Hypothesis: The prevalence of oral HPV among Aboriginal and Torres Strait Islander Australians will be high compared with national-level estimates.

2. Using preliminary data from Aim 1, and information on the prevalence of other risk factors for oropharyngeal cancer in the Aboriginal and Torres Strait Islander population, to estimate burden of HPV-related oropharyngeal cancer among Aboriginal and Torres Strait Islander men and women.

   Hypothesis: The burden among Aboriginal and Torres Strait Islanders of HPV and related oropharyngeal cancer will be high.

3. To estimate the impact of HPV vaccination as currently implemented on rates of cervical and oropharyngeal cancer among Aboriginal and Torres Strait Islander Australians.

   Hypothesis: HPV vaccination will, over time, reduce the burden of cervical and oropharyngeal cancer among Aboriginals and Torres Strait Islanders.

4. To evaluate efficacy and cost-effectiveness of targeted extended HPV vaccination among Aboriginal and Torres Strait Islander Australians, incorporating the effectiveness against both cervical cancer (in females) and oropharyngeal cancer. Different upper age thresholds for targeted extension will be considered.

   Hypothesis: Age-extended HPV vaccination for Aboriginal and Torres Strait Islander Australians will be efficacious; we will estimate an upper age limit at which it would be cost-effective

To achieve the above-mentioned research aims and objectives, the project consisted of two distinct parts (see Figure 3.1) spread out over a span of 5 years, with the research contained within this thesis embedded in part 2 and the last subsection of part 1 (area encircled in red). While Aim 1 and 2 became the focus of the PhD resulting in 3 studies (Chapter 4, 6, 9), attention is also drawn to an additional study from the project (Chapter 10). Five systematic reviews have also been published (2 quantitative, 2 qualitative and 1 diagnostic test of accuracy; Chapter 5, 7, 8, 10), which complement the findings from this project. Other relevant manuscripts have been outlined in the appendix (C, D, E). Due to COVID-19, the clinical examination component had to be removed from the project, thus resulting in modification of the research aims and objectives.

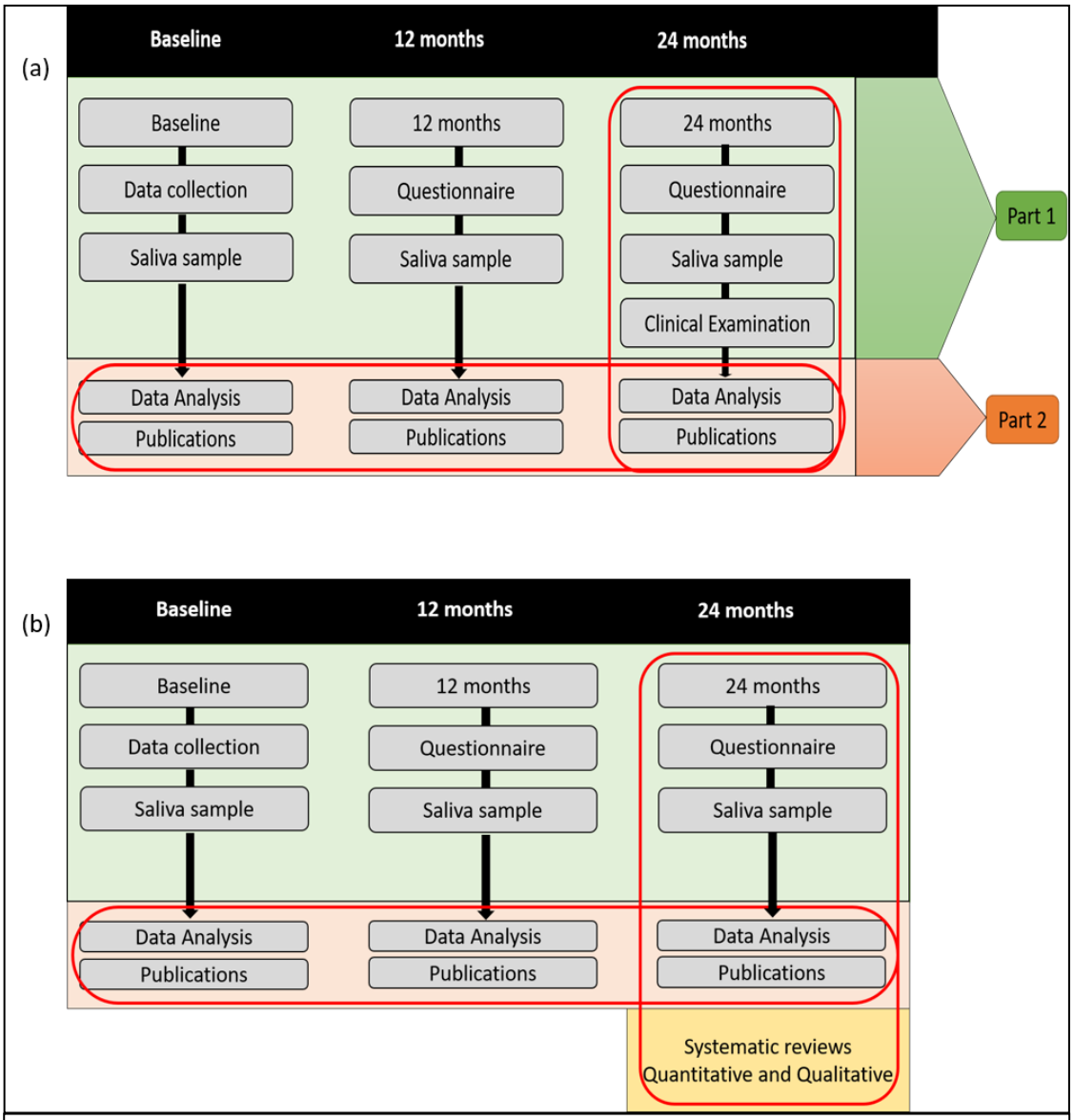


Figure 3.1 (a) Project overview: study plan showing part 1 and 2 with red circled area outlining research contained in this thesis (b) post COVID-19 modifications of research contained within this thesis.

3.3 AIMS AND OBJECTIVES WITHIN THIS THESIS

3.3.1 Aims

The aim of this study was to (1) analyse and correlate socio-demographic variables, oral health behaviours and sexual behaviours with the presence of oral HPV infection and its subtypes (2) evaluate risk factors associated with incidence, persistence and clearance of HPV infection at 12 months (3) evaluate the qualitative experiences of Indigenous populations at a global level regarding HPV infections, vaccines and cancers and (4) evaluate the diagnostic accuracy of a

novel, non-invasive and portable instrument for screening oropharyngeal carcinoma among Indigenous Australians in the subsequent clinical examination phase of the HPV-OPC project.

3.3.2 Objectives

The aims of this thesis will be attained through addressing the following objectives which are:

- Identify the inequalities of oral and general health quality of life among Indigenous and non-Indigenous Australians
- Estimate the prevalence of HPV infection among Indigenous populations at a global level.
- Evaluate risk factors associated with incidence, persistence and clearance of oral HPV infection amongst Australian Indigenous adults at 12 months
- Estimate updated age estimates and gender predilection of Heck's disease and its increased incidence amongst Indigenous populations.
- Undertake a qualitative exploration of HPV infection awareness, and barriers and facilitators of HPV screening amongst Indigenous populations.
- Explore emotions experienced by Indigenous communities after hearing of cancer in the family or community.
- Evaluate diagnostic accuracy of confocal laser endomicroscopy for screening and detection of oral squamous cell carcinoma.

3.4 STUDY POPULATION AND RECRUITMENT:

At baseline, n=1011 Aboriginal South Australian male and female adults were recruited (March 2018 - February, 2019), with a focus on Port Augusta, Whyalla, Port Lincoln, Mount Gambier, Ceduna and Adelaide. Census data indicates approximately 22,000 Aboriginal adults reside in these areas. The investigators have a 13-year relationship with key Aboriginal stakeholder

groups in these locations, who were willing and excited to be part of the study. Recruitment strategies were based on those successfully implemented in the past, as outlined in Figure 3.2.

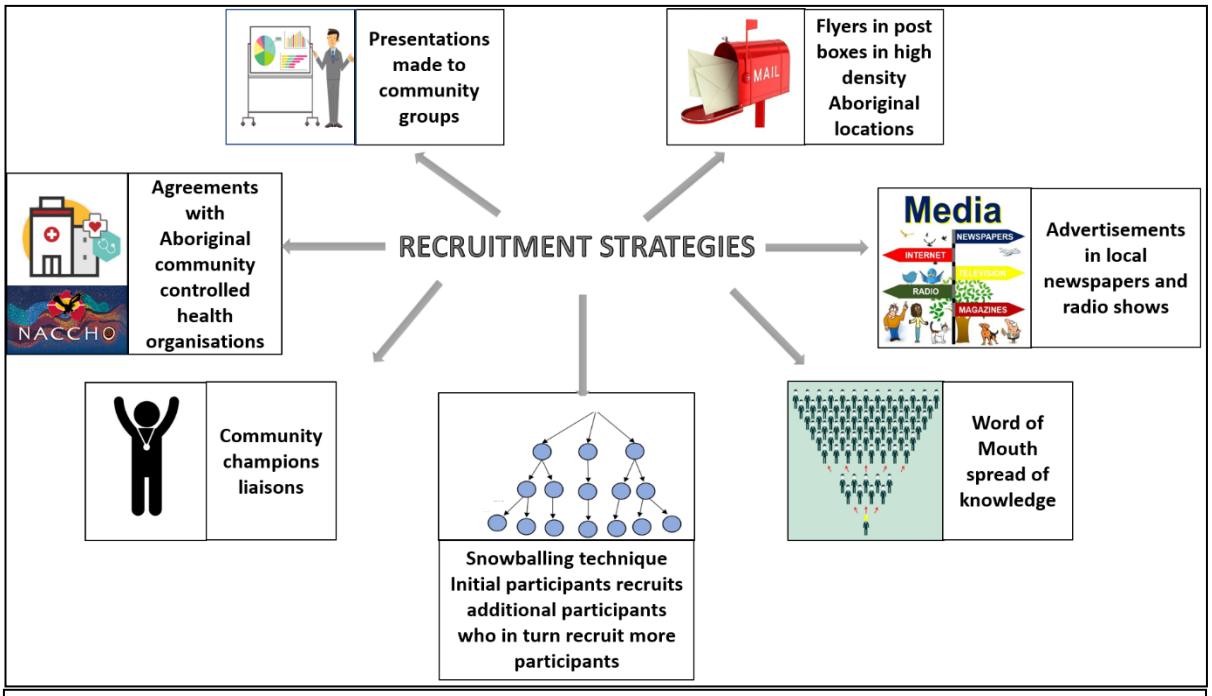


Figure 3.2 - Description of recruitment strategies involved in this project

Retention strategies involved in the project included:

(1) employing staff who were committed to following up participants despite challenges in doing so;

(2) ensuring participants were contacted regularly to ensure accuracy of contact details;

(3) ascertaining contact details of 3 key personnel who may know the whereabouts of participants should the study team be unable to contact them;

(4) sending birthday and Christmas cards to participants and;

(5) facilitating one-on-one relationships between study staff and participants, with study staff ideally seeing each of their participants for each research phase.

3.5 FRAMEWORK OF THE STUDY

This section describes the conceptual framework under-pinning the 7 papers included in this thesis as part of this research. To address the overall aims and proposed research questions, a

mixed methods approach was adopted, as the research questions posed cannot be answered appropriately using an exclusive quantitative approach. The utility of this approach is that different perspectives on the research problem can be obtained from both a qualitative and quantitative approach, thus enabling a more comprehensive investigation. Two strands of data collection and a variety of analysis techniques were incorporated. These included data collected as part of the HPV-OPC project and existing data from peer reviewed scientific literature, thereby enhancing the research validity and allowing a contextually rich dataset. The research methods applied in this thesis illustrated in Figure 3.3.

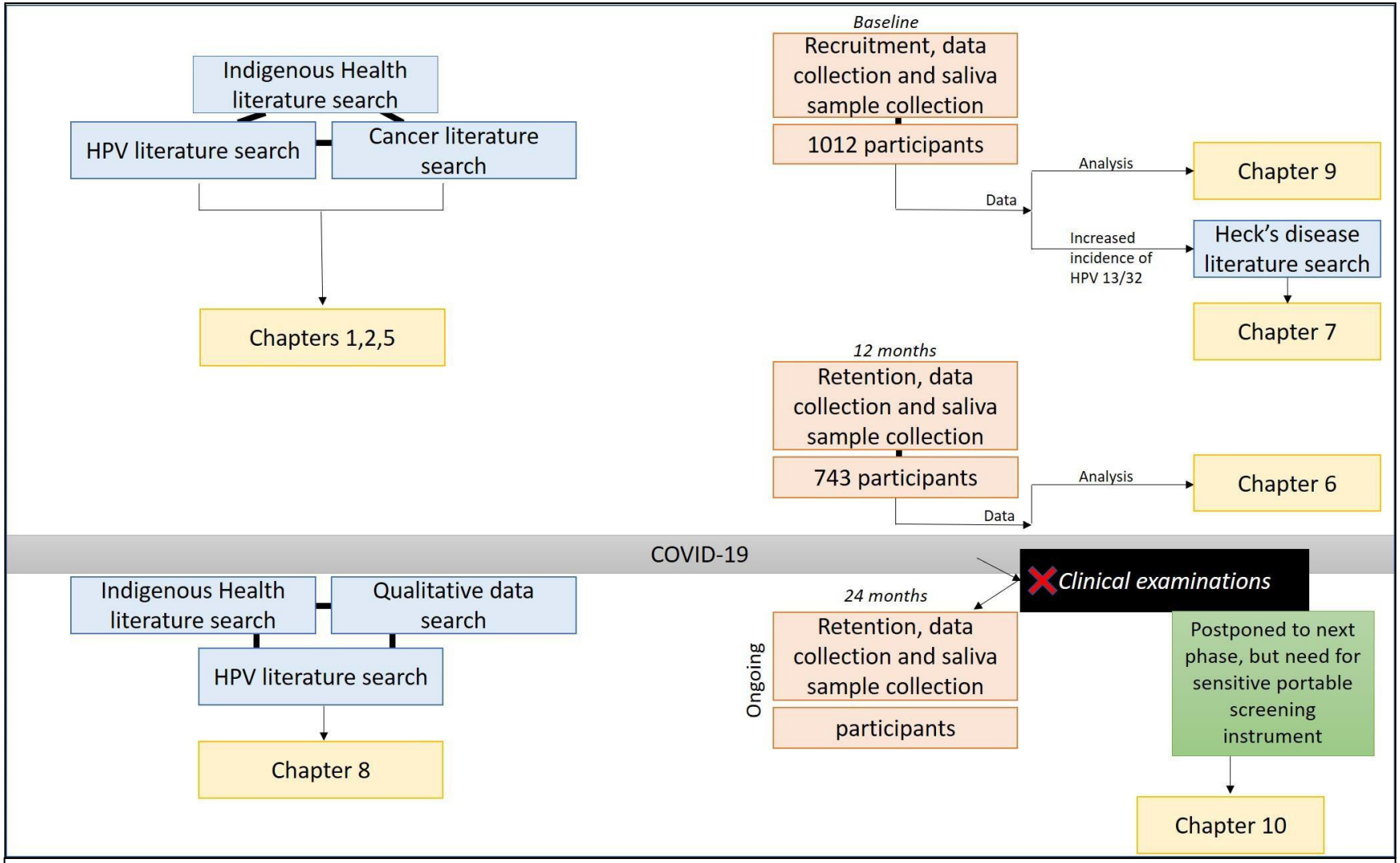


Figure 3.3: Schematic diagram outlining the framework of the studies conducted and presented in this thesis

3.6 FUNDING AND ETHICS

3.6.1 Funding

This project was funded by the National Health and Medical Research Council Grant funding - APP1120215.

3.6.2 Ethics

Ethics approval was obtained from the University of Adelaide Human Research Ethics Committee (H-2016-246) and the Aboriginal Health Council of South Australia (04-17-729)

Participant consent: Each participant was provided with a comprehensive participant information sheet which provided details of the study, the investigators, why they were being asked to participate, how the data will be handled, risks and benefits of participating in the project, complaints and grievances addressal. After providing the information sheet, the research officers explained the details of the project just to ensure that the participant was fully aware of the project and the potential outcomes of their participation in the project. Each participant was asked to sign a consent form which consented their voluntary participation in the study acknowledging the receipt of the project description and aware that the information (de-identified) collected via this project may be published.

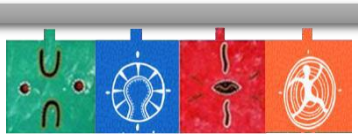
SECTION C: HEALTH INEQUALITIES AMONGST INDIGENOUS AUSTRALIANS

Overview of Section C

This section contains one Chapter which describes general and oral health related quality of life. It compares the two domains between representative Indigenous and Non-Indigenous populations in South Australia. Section C covers the first objective of this thesis and uses data from the baseline findings of the HPV-OPC study and the Dental Care and Oral Health Study. This paper is currently under review.

04

General and oral health related quality of life among Indigenous and non-Indigenous Australians – A comparative research paper



4.1 PREFACE

This study examines general and oral health related quality of life inequalities amongst Indigenous and non-Indigenous Australians. This is an important aspect of this thesis, as it highlights the overarching health inequities at a broad level experienced by Indigenous Australians.

4.2 PUBLICATION DETAILS

Sethi S, Zakershahrak M, Santiago PHR, Jamieson L and Brennan D. General and oral health related quality of life among Indigenous and non-Indigenous Australians – A comparative Research Paper. (BMC Oral Health under Review; submitted April, 2021)

4.3 HIGHLIGHTS

- Indigenous Australians had worse general and oral health-related quality of life compared with non-Indigenous Australians (as measured by EQ-5D and OHIP-14, respectively), but the risk factors for both differed among the population groups
- A higher mean EQ-5D value was observed in the Indigenous compared to the non-Indigenous population. Similarly, higher OHIP-14 scores were observed for the Indigenous group compared with non-Indigenous population.
- Findings demonstrate associations between socioeconomic inequality and Indigenous quality of life.
- For the Indigenous population group, OHIP-14 was higher by 4.2 among those older than 50 years and was 5.5 more among current smokers.

4.4 STATEMENT OF AUTHORSHIP

Statement of Authorship

Title of Paper	General and oral health related quality of life among Indigenous and non-Indigenous Australians – A comparative research paper
Publication Status	☐ Published ☐ Accepted for Publication ☑ Submitted for Publication ☐ Unpublished and Unsubmitted work written in manuscript style
Publication Details	Sethi S, Zakershahrak M, Santiago PHR, Jamieson LM, Brennan D. General and oral health related quality of life among Indigenous and non-Indigenous Australians – A comparative research paper. BMC Oral Health (Under Review)

Principal Author

Name of Principal Author (Candidate)	Sneha Sethi		
Contribution to the Paper	Conceiving of Research Question Data Analysis Manuscript writing Editing and Revisions Paper submission for publication Correspondence with Editors in the publication process		
Overall percentage (%)	75%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	15/09/2021

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);
ii. permission is granted for the candidate in include the publication in the thesis; and
iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Mehrsa Zakershahrak		
Contribution to the Paper	Orientation on formulation of Research Question Data Analysis Manuscript Writing Editing and Revisions		
Signature		Date	15/09/2021

Name of Co-Author	Pedro Henrique Ribeiro Santiago		
Contribution to the Paper	Orientation on formulation of Research Question Data Analysis Manuscript Editing and Revisions		
Signature		Date	15/09/2021

Please cut and paste additional co-author panels here as required.

Name of Co-Author	Lisa Jamieson		
Contribution to the Paper	Orientation on formulation of Research question Revision of Methodology Input in theory application input in Interpretation of Results Revison of Manuscript		
Signature		Date	15/09/2021

Name of Co-Author	David Brennan		
Contribution to the Paper	Orientation on formulation of Research Question Revsion in Methodology Input in theory application Input in interpretation of results Manuscript Editing and Revisions		
Signature		Date	15/09/2021

4.5 PUBLICATION

Title: General and oral health related quality of life among Indigenous and non-Indigenous Australians – A comparative research paper

Authors:

Sneha Sethi[1], Mehrsa Zakershahrak[1], Pedro Henrique Ribeiro Santiago[2], Lisa Jamieson[3], David Brennan[3]

1. PhD Student, Australian Research Centre for Population Oral Health, University of Adelaide, Adelaide, Australia
2. Postdoctoral Research Fellow, Australian Research Centre for Population Oral Health, University of Adelaide, Adelaide, Australia
3. Professor, Australian Research Centre for Population Oral Health, University of Adelaide, Adelaide, Australia

Conflicts of Interest: No conflicts of Interest declared.

Abstract:

Introduction: General and oral health inequalities present an important challenge for public health policy makers, making it of utmost importance to identify these disparities and various risk factors which could impact health outcomes. Indigenous populations have always carried a disproportionate burden of worse health outcomes. The aim of this paper is to describe general and oral health quality of life among Indigenous and the general South Australian population, and to analyse the effect of socioeconomic status and smoking.

Materials and Methods: A general population sample (Dental Care and Oral Health study, conducted in a South Australian population sample) and Indigenous population sample (Human papillomavirus and oropharyngeal carcinoma in Indigenous Australians study) were independently analysed for two outcome variables; oral health related quality of life and general health related quality of life using valid standardised instruments (OHIP-14 and EuroQol respectively). The explanatory variables considered in this study were smoking status, education attained and socio-economic status.

Results: A higher mean EQ5D value was observed in the Indigenous compared to the non-Indigenous population. Similarly, higher OHIP-14 scores were observed for the Indigenous compared with non-Indigenous population. Multiple regression showed statistically significant predictions of EQ-5D from the age, residential location, smoking (current smokers) and health care card ownership in the Indigenous population

Conclusion: The findings demonstrate the importance of more comparative research involving risk factors and health related quality of life among Indigenous and non-Indigenous Australians, and contribute to the knowledge base of impacts of general and oral health-related quality of life.

Introduction:

Disparities and inequalities in health have presented as a significant challenge for health policy making and improvement at a global level (1). Contributing to these inequalities, Indigenous populations carry a disproportionate burden of disease and have worse health outcomes, compared to non-Indigenous people around the world (2,3). These differences have been reported by almost all countries with Indigenous populations, including developed countries such as Australia, New Zealand and Canada (4,5). In Australia, Aboriginal and Torres Strait Islander peoples (hereafter respectfully termed 'Indigenous'), as a small population of the total Australian population, have lower socioeconomic position and associated consequences; such as lower education level, higher percentage of unemployment and low income (6).

The assessment of these disparities, in health and oral health, among Indigenous and non-Indigenous populations has been limited by the absence of high-quality research in several countries (7). Australia is one exception, with inequalities in health and oral health being well recognised (8-11). This has been paramount in both quantifying inequalities in general and oral health and in increasing understanding of the gap between Indigenous and non-Indigenous Australian health and wellbeing (12,13).

Indigenous Australian disadvantage has its roots in the ongoing impacts of colonialism; expropriation of lands, cultural disconnection, material hardship, government policies of assimilation and racism (11). Indigenous Australians have lower life expectancy, 11 to 14 years lower than non-Indigenous Australians (11), which is inextricable linked with poorer health outcomes (13,14-16). There is increased incidence of disability among Indigenous Australians, along with lower quality of life, and higher death rates among younger adults compared with non-Indigenous Australians (11). Associations between socioeconomic status and health are indisputable in any population group (17). Among Indigenous Australian populations,

socioeconomic status, such as source of income and education, substantially impacts the health gap (self-rated health) between Indigenous and non-Indigenous Australians (18).

The Oral Health Impact Profile (OHIP-14) and EuroQol (EQ-5D) are two non-clinical standardised self-rated instruments used by researchers globally to measure health-related quality of life, oral health and general health status (19-21). They are valuable instruments which provide unique information regarding the evaluation and frame-of-reference of individuals about their own health (22).

Socioeconomic status (SES) is defined as an individual or family's economic and social position in society measured by variables including income, education and occupation (23). Socioeconomic inequalities can largely describe variations in health status between different population groups (24,25). There is a growing body of literature highlighting socioeconomic inequality in health in Australia and internationally (26-34).

Tobacco smoking is a pervasive global health problem that has a significant impact on health. It is associated with diseases such as lung cancer, cardiovascular problems, pulmonary disease and complications in pregnancy (35). Estimates suggest that 47% of the Indigenous Australians smoke daily, compared to 21% of non-Indigenous Australians (36). The proportion of Indigenous Australians who smoke is twice that of their non-Indigenous Australians counterparts when stratified by income, education and employment status (37).

In this study, we aim to describe general and oral health quality of life among Indigenous and the general South Australian population, and to analyse the effect of socioeconomic status and smoking. Our hypothesis was that Indigenous Australians would have worse general and oral quality of life compared with non-Indigenous Australians, but that the risk factors for both would be similar for both population groups. This paper could provide useful information in addressing the health gap between Indigenous and non-Indigenous populations.

Materials and Methods

Data collection:

Two datasets with different population samples; Indigenous and general, were used.

For the general population sample, data were collected as a part of the Dental Care and Oral Health Study (DCOHS); a random sample of adults residing in South Australia from the Electoral Roll as a part of the broader longitudinal study, which recorded changes in oral health outcomes according to different pathways of dental care. A total of 12,245 adults aged 18 years or over participated. Data were collected (2015-2016) by a self-completed questionnaire, which was mailed to participants with a primary approach letter and up to four follow-up mailings. Data included information on self-reported general and oral health, health and related behaviours, demographics and socioeconomic variables (age, sex, place of birth, education, occupation, income, financial strain), and psychosocial variables. Ethics approval was obtained from the University of Adelaide Human Research Ethics Committee (H-288-2011) (38).

For the Indigenous sample, data were from the oral human papillomavirus (HPV) and Oropharyngeal Cancer (HPVOC) Study (39). Participants aged 18+ years and who identified as being Indigenous were included. Ethics approval was obtained from the University of Adelaide Human Research Ethics Committee (H-2016-246) and the Aboriginal Health Council of South Australia (04-17-729). All participants provided signed informed consent.

Outcome Variables:

General health related quality of life (HRQoL) and oral health related quality of life (OHRQoL) were measured using the outcome variables: European Quality of Life indicator or EuroQol (EQ-5D) and the Oral health Impact Profile (OHIP-14), respectively.

EQ-5D is a standardised self-reported instrument that assesses health status and health-related quality of life in five dimensions (40). This measure was collected as a 5-level response (EQ-

5D-5L) in the Indigenous dataset, and as a 3-level response (EQ-5D-3L) in the general population dataset. The EQ-5D-3L was responded to on a three-point rating scale ("none"/"no", "some" and "extremely"/"unable"/"confined"), with answers coded in a Likert-type response scale from 0=none to 3=extremely. The calculated sum score ranged from 0 to 15, with higher scores indicating worse quality of life. The EQ-5D-5L was responded to on a five-point rating scale ("no problems", "slight problems", “moderate problems”, “severe problems” and “extreme problems”), with answers coded in a Likert-type response scale from 0=none to 5=extremely. The calculated sum score ranged from 0 to 25, with higher scores indicating worse quality of life.

To equalise the EQ-5D-5L and EQ-5D-3L scores, a four-step parametric test equating procedure was used. Firstly, the Partial Credit Model (41) was used to evaluate whether the EQ-5D-5L and EQ-5D-3L fitted the Rasch model. Since fit of both scales to the Rasch model was established, the second step was to calculate the mean item threshold between the first ("no"/"slight") and second ("slight"/"moderate") thresholds and between the third ("moderate"/"severe") and fourth ("unable/extreme") thresholds of each EQ-5D-5L item. Thirdly, the two EQ-5D-5L mean item thresholds were equated with the two EQ-5D-3L item thresholds using the weighted least squares procedure described by Haebara (42). Fourthly, the equated EQ-5D-5L mean item thresholds were used to calculate expected scores (43) to the three EQ-5D-3L categories. The EQ-5D-5L equated scores are on the same scale and can be directly compared to the EQ-5D-3L scores. The summed score is representative, with higher scores reflecting worse HRQoL. The missing values in outcome variables were excluded due to the effect on the total summed scale.

OHIP-14 is a 14 item, patient-centred standardised global instrument that measures oral health and the impact of oral health, its related behaviours, disabilities and discomfort (in seven dimensions) on wellbeing and quality of life in the previous year (21). The answers were coded in a Likert-type response scale graded from 0=never to 4=very often. The calculated sum score ranged from 0 to 56, with higher scores indicating worse OHRQoL.

Explanatory Variables:

Explanatory variables included socioeconomic status and tobacco smoking status (to express health behaviours). Ownership of a health care card was used as an indicator of socioeconomic status and was coded as card holders and non-holders, with card holders as the reference category. Highest educational attainment, another indicator of socioeconomic status, was categorised as 'high school' and 'trade, tertiary or TAFE'. The references category was 'trade, tertiary or TAFE'. Smoking status was coded as current smokers, former smokers and never smoked; the reference category was non-smokers.

Other variables included in the model were age, gender, location of residence and last dental visit (to reflect access to dental care). Age was dichotomised as groups of above 51 and below 50 years, and residential location was described as either Greater Adelaide or the rest of South Australia (regional). Last dental visit was dichotomised into '<1 year ago' and '1+ years ago'.

Analysis:

The Indigenous participants (23 participants) were removed from the general dataset, and will henceforth be referred to as the non-Indigenous population. Analysis was limited to participants who provided complete responses to the EQ-5D, OHIP-14, tobacco smoking, Health Care Card (HCC) and education attainment. Multivariate analysis of variance (MANOVA) was performed separately with the variables of both datasets, to measure differences in outcomes (OHIP-14 and EQ-5D) by different levels of education, smoking status and other variables. Univariate analysis of variance was then used to assess the main effect of the explanatory variables (socioeconomic status and smoking) on each outcome while controlling for other variables in each population. Parameter estimates were applied to calculate Beta coefficients of different categories of variables. A multiple regression model was run to estimate OHIP-14 and EQ-5D based on education, smoking status and other variables. The non-Indigenous dataset was weighted, SPSS version 27 (IBM Corp.) was used for all the statistical analyses, with statistical differences denoted by non-overlapping 95% confidence intervals.

Results

Sample characteristics

The non-Indigenous population sample comprised 3948 participants, and the Indigenous population sample comprised 897 participants. The mean age for the non-Indigenous and Indigenous samples was 57.7 years (range - 23-91) and 39.3 years (range – 18-82), respectively. Both samples comprised more females; 56% in the non-Indigenous and 66% in the Indigenous sample. Over three quarters (76%) of the non-Indigenous population resided in the Greater Adelaide area compared to 38% of the Indigenous sample. (Table 1)

A higher mean EQ5D value was observed in the Indigenous compared to the non-Indigenous population. Similarly, higher OHIP-14 scores were observed for the Indigenous compared with non-Indigenous population. The highest OHIP-14 scores were observed in the Indigenous sample among those aged 51+ years (state value) followed by current smokers (state value). (Table 2)

The results of multiple regression showed statistically significant predictions of EQ-5D from the age, residential location, smoking (current smokers) and health care card ownership in the Indigenous population; F (8, 888) = 8.205, p < .0005, with an adjusted $R2$ of 0.060 (Table 3). In the general population, EQ-5D was statistically significantly associated with all variables except residential location (F (8, 3939) = 37.269, p < .0005, Adjusted $R2=0.068$). Among the general populations, EQ-5D was 0.229 higher if highest educational attainment was high school and 0.459 more if participants were current smokers.

Among the non-Indigenous population, OHIP-14 scores were higher among males, those whose last dental visit was more than a year ago, those with highest educational attainment of high school, former and current smokers. OHIP-14 scores were lower among those who did not own a health care card (Table 4). For the Indigenous populations, OHIP-14 was higher by 4.2 among those older than 50 years and was 5.539 more among current smokers; F (8, 888) = 6.578, p < .0005, Adjusted $R2$ = 0.047.

Discussion

Our hypothesis proved to be partially true. Indigenous Australians did have worse general and oral quality of life compared with non-Indigenous Australians (as measured by EQ-5D and OHIP-14, respectively), but the risk factors for both differed among the population groups.

Health inequalities are widely recognised concerns in both the public health and social justice systems. Lower quality of life is characterised by poor oral health and worse general health outcomes, leading to inequalities and disparities on the basis of health states. These include ability to be productive in the workplace, to engage meaningfully in community leadership and to have a sense of control over important life decisions. Improving quality of life and understanding factors that contribute to these differences could make a significant contribution towards closing the gap between Indigenous and non-Indigenous health at a global level (44).

Developed countries such as Australia, Canada, New Zealand and the United States have witnessed the negative effects of colonization. Indigenous populations in these countries bear the substantive burden of post-colonial consequences across all aspects of life including education, housing, health, legal rights, social and cultural disparities (45). Poverty, overcrowded homes, lower education status and the struggle to provide for large families has an impact on quality of life (46). Poor nutrition and limited resources lead to an increase in damaging health choices and behaviours, resulting in a disproportionate burden of disease and worse health and oral health outcomes (46).

Our findings demonstrate associations between socioeconomic inequality and Indigenous quality of life. Our findings are corroborated by others in Australia (34,46,47), India (48), South America (49) and Canada (50,51). It has been proposed that causality is bidirectional between low socio-economic status and poor health. Any attempts to modify risk behaviours, such as smoking and consumption of alcohol, without altering socioeconomic disparity will be

ineffective, because of the social and historical determinants which shape the way in which Indigenous Australians live their lives. (52). For example, in our study, ownership of a government healthcare card was associated with poor general and oral health outcomes; indicating existing socio-economic inequality which is, in turn, associated with increased disease prevalence and health-related quality of life (52).

Unavoidable and preventable risk factor is smoking, which has a major influence on health-related quality of life (53). In our study, the proportion of current smokers was higher among the Indigenous population and could possibly influence higher OHIP-14 and EQ-5D scores. Similar general and oral health outcomes using self-rated instruments, with smoking as a risk factor, have been observed (54,55).

Education is closely related to an individual's capacity to be aware of disease and potentially refrain from destructive health behaviours (smoking, alcohol consumption, drug addiction, healthy food habits). Educational attainment is largely a product of early life determinants (for example, parenting, childhood SES), and in our study, the highest educational attainment of the majority of Indigenous participants was high school, while for the general sample, the highest educational attainment for the majority of participants was trade, university or TAFE.

Strength of this study lies in the measurements of both general health and oral health parameters using valid, standard instruments that are common to both study populations. The limitation of this study was the absence of representative studies to corroborate findings in the existent literature. Also, the associations found did not imply causality. The response rates could be a limitation, but response numbers were a strength.

Comparative research can be limited as representative population studies often have small numbers of Indigenous persons, while here we were able to compare data across two studies from the same geographic area from around the same time period.

Conclusion

This study has highlighted substantial inequities in general and oral health related quality of life among Indigenous and non-Indigenous populations in Australia. The findings demonstrate the importance of more comparative research involving risk factors and health related quality of life among Indigenous and non-Indigenous Australians, and contribute to the knowledge base of impacts of general and oral health-related quality of life.

Conflicts of Interest: No conflicts of Interest declared.

Data sharing statement: The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Author Contribution statement:

SS and MZ conceived the idea. SS developed the theory and MZ helped with the computations. DB and LJ verified the analysis. DB and LJ encouraged SS and MZ to investigate and have supervised the work. PHRS conducted the Rasch analysis and validated the EQ-5D-3L in the Indigenous population dataset. All authors have discussed the results and contributed to the final manuscript.

References:

1. Marmot M, Allen JJ. Social determinants of health equity. Am J Public Health. 2014 Sep;104;(Suppl 4): S517-9. doi: 10.2105/AJPH.2014.302200.
2. Alderete E. The Health of Indigenous Peoples. Geneva, Switzerland: World Health Organization; 1999

3. Nettleton C, Napolitano DA, Stephens C. An Overview of Current Knowledge of the Social Determinants of Indigenous Health. Geneva, Switzerland: World Health Organization, Commission on Social Determinants of Health; 2007
4. Stephens C, Nettleton C, Porter J, Willis R, Clark S: Indigenous peoples' health: why are they behind everyone, everywhere? Lancet. 2010,366:10-13.
5. United Nations Department of Economic and Social Affairs: State of the World's Indigenous Peoples. 2009, New York: United Nations
6. Brennan DS, Roberts-Thomson KF, Spencer AJ. Oral health of Indigenous adult public dental patients in Australia. Aust Dent J. 2007 Dec;52(4):322-8. doi: 10.1111/j.1834-7819. 2007.tb00509. x.
7. Gracey M, King M. Indigenous health part 1: determinants and disease patterns. Lancet. 2009;374(9683):65–75
8. Vos T, Barker B, Begg S, Stanley L, Lopez AD. Burden of disease and injury in Aboriginal and Torres Strait Islander Peoples: The Indigenous health gap. Int J Epidemiol. 2009;38(2):470–477
9. Pink B, Allbon P. The Health and Welfare of Australia's Aboriginal and Torres Strait Islander Peoples, 2008. Canberra: Australian Bureau of Statistics and Australian Institute of Health and Welfare; 2008
10. Zhao Y, You J, Wright J. Health inequity in the Northern Territory, Australia. Int J Equity Health 2013;12,79.
11. Harford J, Spencer AJ, Roberts-Thomson KF. Oral health. In: Thomson N., ed. The health of Indigenous Australians. Oxford: Oxford University Press, 2003.
12. Hopcraft MS, Morgan MV. Dental caries experience in a young adult military population. Aust Dent J 2003; 48:125–129.

13. Brennan DS, Spencer AJ. Changes in caries experience among public dental patients between 1995/96 and 2001/02.Aust N Z J Public Health 2004; 28:542–548
14. Schamschula RG, Cooper MH, Wright MC, Agus HM, Un PS. Oral health ofadolescent and adult Australian Aborigines. Comm Dent Oral Epidemiol 1980; 8:370–374.
15. Brennan DS, Carter KD. Adult access to dental care—Indigenous Australians. AIHW Cat. No. DEN 40. Adelaide: The University of Adelaide (AIHW Dental Statistics and Research Series No. 16), 1998.
16. Australian Bureau of Statistics and Australian Institute of Health and Welfare. The Health and Welfare of Australia's Aboriginal and Torres Strait Islander Peoples, 2003. ABS Cat. no. 4704.0 and AIHW Cat. no. IHW11. Canberra: ABS and AIHW, 2003.
17. Lynch J. Social epidemiology: some observations about the past, present and future. Australas Epidemiol. 2000;7(3):7–15.
18. Booth AL, Carroll N. Economic status and the Indigenous/non-Indigenous health gap. Econ Lett. 2008;99(3):604–606
19. Slade GD, Spencer AJ: Development and evaluation of the oral health impact profile. Community Dent Health 1994, 11:3-11
20. Gift HC, Atchison KA: Oral health, health, and health-related quality of life. Med Care 1995, 33: NS57–NS77.
21. Slade GD: Derivation and validation of a short-form oral health impact profile. Community Dent Oral Epidemiol 1997; 25:284-290.
22. Bowling A. Measuring disease. A review of disease-specific quality of life measurement scales Second edition. Buckingham: Open University Press; 2001.
23. Fayers P, & Sprangers MA. Understanding self-rated health. The Lancet 2002;359(9302):187-188.

24. Spicker P, Leguizamon S, Gordon D. Poverty: an international glossary. Bergen: CROP; 2007.
25. Wagstaff A. Poverty and health sector inequalities. Bull World Health Organ. 2002; 80:97–105.
26. Gakidou EE, Murray CJL, Frenk J. Defining and measuring health inequality: an approach based on the distribution of health expectancy. Bull World Health Organ. 2000; 78:42–54.
27. Draper G, Turrell G, Oldenburg B. Health inequalities in Australia: mortality. Canberra: Queensland University of Technology and AIHW; 2004.
28. Marmot M. Social determinants of health inequalities. Lancet. 2005; 365:1099–1104.
29. Wagstaff A, Doorslaer E. Overall versus socioeconomic health inequality: a measurement framework and two empirical illustrations. Health Econ. 2004; 13:297–301. doi: 10.1002/hec.822. [PubMed] [CrossRef] [Google Scholar]
30. Carson EB, Dunbar T, Chenhall RD. Social determinants of indigenous health. Sydney: Allen & Unwin; 2007.
31. Power C, Manor O, Matthews S. The duration and timing of exposure: effects of socioeconomic environment on adult health. Am J Public Health. 1999; 89:1059–1065.
32. Najman JM, Aird R, Bor W, O'Callaghan M, Williams GM, Shuttlewood GJ. The generational transmission of socioeconomic inequalities in child cognitive development and emotional health. Soc Sci Med. 2004; 58:1147–1158.
33. Australian Institute of Health and Welfare. Health in rural and remote Australia. Canberra: AIHW; 1998.
34. Australian Institute of Health and Welfare. Rural, regional and remote health indicators of health status and determinants of health. Canberra: AIHW; 2008.

35. Fiore MC, Bailey WC, Cohen SJ, Dorfman SF, Goldstein MG, Gritz ER, Heyman RB, al. E. Treating Tobacco Use and Dependence, Clinical Practice Guideline. Rockville, MD: U.S. Department of Health and Human Services; 2000.
36. Australian Institute of Health and Welfare. The health and welfare of Australia's Aboriginal and Torres Strait Islander people, an overview 2011. Canberra: AIHW; 2011.
37. Scollo MM Winstanley MH, editor. Tobacco in Australia: Facts and Issues. 3. Melbourne: Cancer Council Victoria; 2008.
38. Song Y, Luzzi L, Chrisopoulos S, Brennan D. Dentist-patient relationships and oral health impact in Australian adults. Community Dent Oral Epidemiol. 2020; 00:1–8.
39. Jamieson L, Garvey G, Hedges J, Mitchell A, Dunbar T, Leane C et al. Human Papillomavirus and Oropharyngeal Cancer Among Indigenous Australians: Protocol for a Prevalence Study of Oral-Related Human Papillomavirus and Cost-Effectiveness of Prevention. JMIR Res Protoc. 2018 Jun 8;7(6): e10503.
40. EuroQol Research Foundation. EQ-5D-3L User 2018. Available from: http://euroqol.org/publications/userguides
41. Masters, GN. A Rasch model for partial credit scoring. Psychometrika 1982;47(2):149-174.
42. Haebara, T. Equating logistic ability scales by a weighted least squares method. Japanese Psychol Res 1980;22(3):144-149.
43. Mesbah, M., & Kreiner, S. (2012). Rasch models for ordered polytomous items. Rasch models in health, 27-42.
44. Stephens C, Nettleton C, Porter J, Willis R, Clark S: Indigenous peoples' health: why are they behind everyone, everywhere? Lancet. 2010, 366: 10-13.

45. United Nations Department of Economic and Social Affairs: State of the World's Indigenous Peoples. 2009, New York: United Nations
46. Markwick A, Ansari Z, Sullivan M. et al. Inequalities in the social determinants of health of Aboriginal and Torres Strait Islander People: a cross-sectional population-based study in the Australian state of Victoria. Int J Equity Health 2014;13,91.
47. Shepherd CC, Li J, Zubrick SR. Social gradients in the health of Indigenous Australians. Am J Public Health. 2012;102(1):107-117.
48. Subramanian SV, Smith GD, Subramanyam M. Indigenous Health and Socioeconomic Status in India. PLoS Med 2006;3(10): e421.
49. Servan-Mori E, Torres-Pereda P, Orozco E. et al. An explanatory analysis of economic and health inequality changes among Mexican indigenous people, 2000-2010. Int J Equity Health 2014;13,21.
50. Veenstra G. Racialized identity and health in Canada: Results from a nationally representative survey. Social Science & Medicine, 2009;69(4):538-542. https://doi.org/10.1016/j.socscimed.2009.06.009.
51. Frohlich KL, Ross N, Richmond C. Health disparities in Canada today: Some evidence and a theoretical framework. Health Policy, 2006;79(2-3):132-143.
52. Williams SD, Parker ED, Jamieson LM. Oral health-related quality of life among rural-dwelling indigenous Australians. Aust Dent J. 2010 Jun;55(2):170-6.
53. World Health Organization. The world health report: health systems financing: the path to universal coverage. Geneva: WHO; 2010.
54. Sagtani RA, Thapa S. & Sagtani A. Smoking, general and oral health related quality of life – a comparative study from Nepal. Health Qual Life Outcomes 2020;18(257).
55. Bakri, NN; Tsakos, G; Masood, M; (2018) Smoking Status and Oral Health-related Quality of Life Among Adults in the United Kingdom. Br Dent J 2018;225(2):153-158.

Table 1: Characteristics of the non-Indigenous and Indigenous study participants

	Non- Indigenous Population	Indigenous Population
Total	3948	897
Age (years)		
Mean (SE)	57.7 (0.2)	39.3 (0.4)
Range	23 – 91	18-82
50 years and below	1251 (31.7%)	663 (73.9%)
51 and above	2697 (68.3)	234 (26.1%)
Sex		
Male	1722 (43.6%)	305 (34.0%)
Female	2226 (56.4%)	592 (66.0%)
Location		
Greater Adelaide	2988 (75.7%)	336 (37.5%)
Rest of South Australia	960 (24.3%)	561 (62.5%)
Last Dental Visit		
Less than a year ago	2458 (62.3%)	413 (46.0%)
More than a year ago	1490 (37.7%)	484 (54.0%)
Education		
High School	1761 (44.6%)	611 (68.1%)
Trade, University or TAFE	2187 (55.4%)	286 (31.9%)
Smoking Status		
Non-Smoker	2171 (55%)	273 (30.4%)
Former	1332 (33.7%)	145 (16.2%)
Current	445 (11.3%)	479 (53.4%)
Health Care Card		
Yes	702 (17.8%)	684 (76.3%)
No	3246 (82.2%)	213 (23.8%)

Table 2: Descriptive statistics of EQ-5D and OHIP-14 by sample characteristics for non-Indigenous and Indigenous study participants

	Non- Indigenous Population			Indigenous Population			Non-Indigenous			Indigenous Population		
	EQ–5D			EQ–5D			OHIP-14			OHIP–14		
		95% C.I.			95% C.I.			95% C.I.			95% C.I.	
	Mean	L.B.	U.B.	Mean	L.B.	U.B.	Mean	L.B.	U.B.	Mean	L.B.	U.B.
Age												
50 y & below	0.67	0.61	0.73	1.13	0.99	1.28	5.85	5.41	6.31	16.03	15.04	17.03
51 & above	1.12	1.07	1.18	2.26	1.89	2.64	6.62	6.28	6.98	19.54	17.75	21.34
Sex												
Male	0.95	0.89	1.02	1.44	1.19	1.70	6.15	5.75	6.56	16.41	15.03	17.81
Female	0.99	0.94	1.05	1.42	1.24	1.60	6.56	6.56	6.95	17.22	16.10	18.35
Location												
Greater Adelaide	0.95	0.91	1.00	1.58	1.33	1.83	6.25	5.94	6.57	16.06	14.77	17.37
Rest of SA	1.04	0.96	1.13	1.33	1.16	1.52	6.77	6.19	7.36	17.48	16.31	18.65
Last Dental Visit												
One year or Less	0.88	0.84	0.94	1.48	1.27	1.69	5.75	5.43	6.08	17.59	16.32	18.87
More than a year ago	1.12	1.05	1.20	1.38	1.18	1.59	7.41	6.91	7.92	16.40	16.40	15.20
Education												
High School	1.18	1.12	1.25	1.37	1.20	1.55	7.25	6.80	7.71	17.48	16.37	18.59
Trade, Uni	0.81	0.76	0.86	1.54	1.27	1.81	5.68	5.35	6.02	15.82	14.42	17.23
Smoking Status												
Non-Smoker	0.80	0.76	0.86	1.25	0.99	1.51	5.15	4.84	5.47	13.73	12.20	15.26
Former	1.13	1.06	1.21	1.39	1.03	1.77	6.75	6.27	7.23	16.27	14.12	18.43
Current	1.35	1.21	1.50	1.54	1.34	1.74	11.26	10.07	12.46	18.99	17.79	20.20
Health Care Card												
Yes	1.31	1.20	1.43	1.53	1.36	1.72	8.03	7.26	8.81	17.28	16.27	18.29
No	0.90	0.86	0.95	1.07	0.83	1.32	6.02	5.73	6.32	15.89	14.12	17.67

Table 3 Adjusted models of EQ-5D by sample characteristics for non-Indigenous and Indigenous study participants

	Non- Indigenous Population			Indigenous Population		
	EQ–5D			EQ–5D		
	B-coeff	**C.I. (L.B.)**	**C.I. (U.B.)**	**B – coeff**	**C.I. (L.B.)**	**C.I. (U.B.)**
Constant	0.633**	0.279	0.987	0.534 NS	-0.618	1.687
Age *(ref. Category: Below 50 years)*	0.400**	0.310	0.491	1.201**	0.869	1.533
Sex *(ref. Category: Female)*	-0.135**	-0.217	-0.053	0.070 NS	-0.236	0.377
Location *(ref. Category: Greater Adelaide)*	0.012 NS	-0.082	0.107	-0.309*	-0.608	-0.009
Last Dental Visit *(ref. Category: less than a year ago)*	0.219**	0.134	0.303	-0.216 NS	-0.508	0.077
Education *(ref. Category: Above High School)*	0.229**	0.146	0.313	-0.199 NS	-0.516	0.118
Smoking Status: Former Smokers *(ref. Category: Non-Smoker)*	0.224**	0.133	0.315	0.067 NS	-0.373	0.507
Smoking Status: Current Smokers *(ref. Category: Non-Smoker)*	0.459**	0.326	0.592	0.345*	0.015	0.675
Health Care Card *(ref. Category: Yes)*	-0.319**	-0.425	-0.213	-0.374*	-0.723	-0.024
Model Adjusted R-Squared	0.068			0.060		

** P<0.01
* P<0.05
NS: Not Significant

Table 4: Adjusted models of OHIP-14 by sample characteristics for non-Indigenous and Indigenous study participants

	Non- Indigenous Population			Indigenous Population		
	OHIP-14			OHIP-14		
	B-coeff	**95% C.I. (L.B.)**	**95% C.I. (U.B.)**	**B–coeff**	**95% C.I. (L.B.)**	**95% C.I. (U.B.)**
Constant	9.182**	6.799	11.564	17.803**	10.879	24.727
Age *(ref. Category: 50 years and below)*	0.604 NS	-0.005	1.213	4.200**	2.204	6.196
Sex *(ref. Category: Female)*	-0.895**	-1.446	-0.344	-0.924 NS	-2.766	0.918
Location *(ref. Category: Greater Adelaide)*	0.227 NS	-0.408	0.862	0.908 NS	-0.891	2.707
Last Dental Visit *(ref. Category: less than a year ago)*	1.202**	0.633	1.772	-1.717 NS	-3.473	0.040
Education *(ref. Category: High School)*	0.880**	0.319	1.442	1.329 NS	-0.575	3.233
Smoking Status: Former Smokers *(ref. Category: Non-Smoker)*	1.430**	0.820	2.041	2.326 NS	-0.317	4.968
Smoking Status: Current Smokers *(ref. Category: Non-Smoker)*	5.745**	4.850	6.640	5.539**	3.556	7.522
Health Care Card *(ref. Category: Yes)*	-1.463**	-2.176	-0.749	0.300 NS	-1.798	2.398
Model Adjusted R-Squared	0.058			0.047		
** P<0.01 * P<0.05 NS: Not Significant						

End of Publishe

SECTION D: HUMAN PAPILLOMAVIRUS INFECTION IN INDIGENOUS POPULATIONS

Overview of Section D

This section contains three chapters which focus on HPV infection amongst Indigenous populations. It comprises: (1) global prevalence of HPV infection;(2) risk factors affecting the incidence, persistence and clearance of oral HPV infections and; (3) a critical review of Heck's Disease. This section covers the second, third and fourth objective of this thesis and uses data from the baseline and 12-month follow-up of the HPV-OPC study. Two of the three included papers are published and the third is under review.

This section highlights the burden of HPV infection among Indigenous population groups and emphasises the unique findings of the HPV-OPC study.

05

A systematic review and meta-analysis of the prevalence of human papillomavirus infection in Indigenous populations - A Global Picture

5.1 PREFACE

The study (Study 2) presented in this Chapter is the first of three studies in this section that address the second objective of this thesis. While the study in the previous section examined the inequalities of general and oral health related quality of life amongst Indigenous and non-Indigenous Australians, this section examines HPV infection.

This study is the first to investigate the prevalence of HPV infection amongst Indigenous populations at a global level. This is a systematic review followed by a meta-analysis, using cutting-edge appraisal and data extraction tools

5.2 PUBLICATION DETAILS

This paper has been published in the Journal of Oral Pathology and Medicine as: Sethi S, Ali A, Ju X, Antonsson A, Logan R, Canfell K, Smith M, Garvey G, Hedges J, Jamieson L. A systematic review and meta-analysis of the prevalence of human papillomavirus infection in Indigenous populations - A Global Picture. J Oral Pathol Med. 2021 May 18. doi: 10.1111/jop.13201. Epub ahead of print. PMID: 34008187.

5.3 HIGHLIGHTS

- The systematic review and meta-analysis reveal a pooled global prevalence of 34.2% of HPV infection in Indigenous populations highlighting a high pooled prevalence in Indigenous populations, as compared to a previously reported HPV prevalence in non-Indigenous populations.
- The most prevalent HPV type seen was HPV 16 in 21 studies out of 41 (51.2%). The second most common type was HPV 18 in 4 studies (9.7%)
- The high pooled global prevalence of HPV infection in Indigenous populations was irrespective of geographical location.

5.4 STATEMENT OF AUTHORSHIP

Statement of Authorship

Title of Paper	A systematic review and meta-analysis of the prevalence of human papillomavirus infection in Indigenous populations - A Global Picture
Publication Status	☑ Published ☐ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and Unsubmitted work written in manuscript style
Publication Details	Sethi S, Ali A, Ju X, Antonsson A, Logan R, Canfell K, Smith M, Garvey G, Hedges J and Jamieson L. A systematic review and meta- analysis of the prevalence of human papillomavirus infection in Indigenous populations – A Global Picture. J Oral Pathol Med. 2021;00:1– 12. https://d o i .org/10.1111/jop.13201

Principal Author

Name of Principal Author (Candidate)	Sneha Sethi		
Contribution to the Paper	Conceiving of Research question Data Analysis Manuscript writing Editing and Revisions Paper submission for publication Correspondence with Editors in the publication process		
Overall percentage (%)	75%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	20/07/2021

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);
ii. permission is granted for the candidate in include the publication in the thesis; and
iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Anna Ali		
Contribution to the Paper	Input in Methodology Data Analysis Interpreation and Writing of results Revision of Manuscript		
Signature		Date	17 Sep 2021

Name of Co-Author	Xiangqun Ju		
Contribution to the Paper	Orientation on formulation of Research question Revision of Methodology Input in theory application Input in Interpretation of results Revision of Manuscript		
Signature		Date	17 Sep 2021

Please cut and paste additional co-author panels here as required.

Name of Co-Author	Annika Antonsson		
Contribution to the Paper	Revision of Methodology Input in theory application input in Interpretation of Results Revison of Manuscript		
Signature		Date	17 Sep 2021

Name of Co-Author	Richard Logan		
Contribution to the Paper	Revision of Methodology Input in theory application Input in Interpretation of results Revision of Manuscript		
Signature	Richard Logan	Date	20 Sept 2021

Name of Co-Author	Karen Canfell		
Contribution to the Paper	Revision of Methodology Input in theory application input in Interpretation of Results Revison of Manuscript		
Signature		Date	17 Sep 2021

Name of Co-Author	Megan Smith		
Contribution to the Paper	Revision of Methodology Input in theory application Input in Interpretation of results Revision of Manuscript		
Signature		Date	17 Sep 2021

Name of Co-Author	Gail Garvey		
Contribution to the Paper	Revision of Methodology Input in theory application input in Interpretation of Results Revison of Manuscript		
Signature		Date	17 Sep 2021

Name of Co-Author	Joanne Hedges		
Contribution to the Paper	Revision of Methodology Input in theory application Input in Interpretation of results Revision of Manuscript		
Signature		Date	17 Sep 2021

Name of Co-Author	Lisa Jamieson		
Contribution to the Paper	Orientation on formulation of Research question Revision of Methodology Input in theory application input in Interpretation of Results Revison of Manuscript		
Signature		Date	17 Sep 2021

5.5 PUBLICATION

Received: 25 August 2020 | Revised: 4 May 2021 | Accepted: 7 May 2021

DOI: 10.1111/jop.13201

REVIEW

Journal of Oral Pathology & Medicine WILEY

A systematic review and meta-analysis of the prevalence of human papillomavirus infection in Indigenous populations – A Global Picture

Sneha Sethi[1] | Anna Ali[2] | Xiangqun Ju[1] | Annika Antonsson[3] | Richard Logan[4] | Karen Canfell[5] | Megan Smith[5] | Gail Garvey[6] | Joanne Hedges[1] | Lisa Jamieson[1]

[1]Australian Research Centre for Population Oral Health, Adelaide Dental School, University of Adelaide, Adelaide, SA, Australia

[2]Robinson Research Institute, University of Adelaide, Adelaide, SA, Australia

[3]QIMR Berghofer Medical Research Institute, QIMR Berghofer Medical Research Institute, Brisbane, Qld, Australia

[4]Adelaide Dental School, University of Adelaide, Adelaide, SA, Australia

[5]Cancer Council of New South Wales, Sydney, NSW, Australia

[6]Menzies School of Health Research, Charles Darwin University, Darwin, NT, Australia

Correspondence
Sneha Sethi, Australian Research Centre of Population Oral Health, Adelaide Dental School, University of Adelaide, Adelaide, SA 5000, Australia.
Email: sneha.sethi@adelaide.edu.au

Funding information
This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Abstract

Background and Aim: Recent trends have shown a decline in the rates of human papillomavirus (HPV)-associated cervical cancer in the vaccinated population but there has been a spike in the HPV-associated oropharyngeal, anal and penile cancers in the majority of the unvaccinated population which are young and middle-aged males. Indigenous populations at an international level carry a disproportionate burden of most diseases. The aim of this meta-analysis was to ascertain the worldwide prevalence of HPV infection in Indigenous populations stratified by sex and site and to document the most commonly reported HPV types.

Methods: Published articles on HPV infection in Indigenous populations from PubMed, Scopus, EMBASE and Web of Science were systematically searched from inception until 23 December 2019.

Results: A total of 41 studies were included in the final analysis. The pooled worldwide prevalence of HPV infection (for both oral and genital sites, both males and females) in Indigenous populations was 34.2% (95% CI: 28.9%–39.8%). Subgroup analysis (geographical) showed that the pooled prevalence for African Indigenous, American Indigenous and Asian-Oceanic Indigenous populations were 33.0% (95% CI: 12.8%–57.1%), 33.0% (95% CI: 27.4%–38.9%) and 33.3% (95% CI: 0.17.5%–51.3%), respectively.

Conclusion: There are not enough data on the burden of the infection carried by males especially with respect to highly suspicious sites like oropharynx. Also, we conclude an overall high prevalence of HPV infection in the Indigenous populations and increasing their susceptibility to benign and malignant manifestations of HPV.

KEYWORDS
cervical cancer, human papillomavirus, Indigenous, oropharyngeal cancer, systematic review

1 | INTRODUCTION

Human papillomavirus (HPV) infection and its concomitant expressions, both benign and malignant, have gained significant public attention at the international level in recent decades. HPV infection has been recognized for its carcinogenic potential targeting the mucous membranes of the cervix, penis, vulva, vagina, anus and oropharynx (including the base of the tongue and tonsils).[1] Reportedly, more than 290 million women worldwide are infected with HPV, which corresponds to 570 000 cases of cervical cancer and 311 000 associated deaths worldwide.[1] The incidence of HPV-related oropharyngeal squamous cell carcinoma in men is rapidly increasing, having overpassed rates of cervical cancer in women in both the United Kingdom[2] and the United States.[3] This has been possible due to highly effective cervical screening programmes and aggressive vaccination programmes for females in these countries; this aggressive approach has led to a desirable reduction in cervical cancer rates by more than 50%.[2,3]

Extensive research has been undertaken with respect to HPV infection, both at a basic science/molecular level and at a population/epidemiological level. Although preventive vaccines have been available in the market since 2006,[4] statistics[5,6] demonstrate a sharp spike in the number of cases reporting with HPV-associated oropharyngeal, anal and penile lesions.[4-6] A systematic review in 2016 demonstrated that while substantial proportions of women from high- and middle-income countries were being vaccinated, women in low-income countries (or regions) (who are potentially at a higher risk) were unable to access the vaccine, but more recently steps are being taken to rectify this situation.[7,8] These studies demonstrate growing inequalities in both the distribution of vaccine and uptake. Because of this, wholesale efforts are being made to create awareness and make vaccinations available to many disadvantaged communities.[9-11] WHO has launched a cervical cancer elimination strategy in May 2020 with three main objectives of preventing, screening and treating HPV-associated cervical cancers; all countries are to vaccinate 90% women, screen 70% women and treat 90% of the invasive cancers by the year 2030.[8]

The United Nations Indigenous Peoples' Partnership defines being 'Indigenous' as 'people with a historical continuity with pre-invasion and pre-colonial societies that developed on their territories, and who consider themselves distinct from other sectors of the societies now prevailing on those territories'. Indigenous populations, who represent 370 million people from across 70 countries, experience health inequalities in ways that are unique and separate to the inequalities experienced by other marginalized groups. This is largely due to colonial influences that have resulted in sustained loss of lands, identity, languages and the control to live life in a way that is meaningful to many Indigenous persons. In many countries, Indigenous groups have been victims of sustained discrimination and marginalization, with policies often focussing on assimilation and, in some cases, cultural annihilation.[12,13] In a report using the 2015 Human Development Index, a composite index of life expectancy, education and per capita income, Australia ranked 2nd, the United States and Canada both ranked 10th, New Zealand ranked 13th and Brazil ranked 75th. However, when Indigenous Australian populations were considered in isolation, the Australian ranking dropped to 122nd. The international community now recognizes that special measures are required to protect the rights of Indigenous groups and to maintain their distinct cultures and way of life.[14] Most countries do not officially recognize their Indigenous groups and have inaccurate or no published statistical data for these people. In almost every country, Indigenous people are over-represented among the poor and disadvantaged, especially in developed countries.[15]

We aimed to review the prevalence of HPV infection in Indigenous populations at an international level. Specific research questions included the following: (1) What is the overall prevalence of HPV infection in Indigenous populations at an international level stratified by sex, site and geographic locations? And (2) what are the most common HPV types reported?

2 | METHODS

This systematic review and meta-analysis have been registered in PROSPERO (CRD number: CRD42020164440) and were conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (Appendix S1).[16]

2.1 | Data sources and searches

A structured literature search was performed using the search engines PubMed, SCOPUS, Web of Science and EMBASE from inception until 23 December 2019. The search strategy included a combination of subject terms and free text terms, and these terms were combined with 'OR' and 'AND' operators. The search comprised the following terms: (first nation/first nations/pacific islander/pacific islanders/torres strait islander/torres strait islanders/aborigin/alaska*/aleut*/amerind*/arctic/Aymara/bushmen/chukchi/chukotka*/circumpolar/eskimo*/greenland*/hmong/indian*/indigen*/inuit*/inupiaq/Inupiat/Khanty/maori*/mapuche/metis/native*/Navaho*/navajo*/nenets/quechua/saami/sami/samoan*/siberia*/skolt/tribal/tribe*/xingu*/yup'ik/yupik/zuni/"African continental ancestry group"/"African continental ancestry group"/"Asian continental ancestry group"/"Health Services, Indigenous"/"Oceanic ancestry group"/"arctic regions"/"ethnic groups"). The reference lists of all relevant articles were checked to identify any additional studies.

2.2 | Study selection

The inclusion criteria for articles to be included were predefined (Figure 1). We considered all observational studies (cross-sectional, cohort and case-control). Studies involving secondary evidence, such as systematic reviews, were excluded. Studies were not excluded on the basis of sample size, as later on we stratified it on

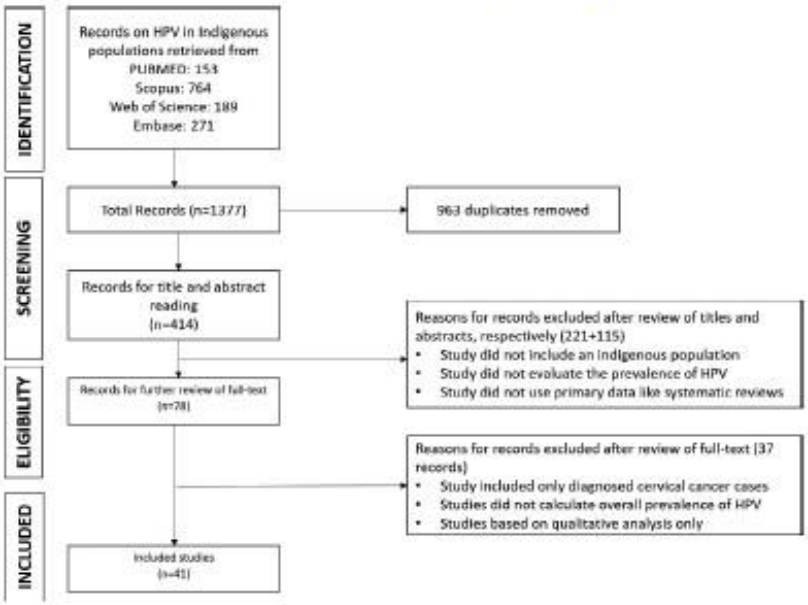


FIGURE 1 Flowchart depicting the study selection to be included in the systematic review

the basis of number of participants. Case reports, case studies and interventional studies (eg clinical trials) were excluded. The titles and abstracts were retrieved from all studies and were analysed by two independent reviewers (SS and A. Ali). Disagreements were solved by discussion, consensus or involving a third reviewer (LJ). The full texts of all selected studies were collected and the aforementioned inclusion criteria were applied. We removed all duplicates and excluded studies which did not include Indigenous populations, were not available in English or had no full-text available.

2.3 | Data extraction and quality assessment

The included studies were 2 case-control studies, 5 cohort studies and 34 cross-sectional studies. In the cohort studies, we included the baseline data only, and in case of two or more studies using the same data, we selected one study with the largest sample size for more representative numbers. The methodological quality and risk of bias were evaluated and scored independently by two reviewers (SS and A. Ali) using the National Institute of Health (NIH) quality assessment tool and Newcastle-Ottawa scale (NOS). The quality of the outcome was summarized using a system with guidance from the GRADE (Grading of Recommendations, Assessment, Development and Evaluations)[17] approach: high, moderate or low quality. In case of NIH assessment, each question was graded as one point, with a response of 'Yes' and 'N.A' as 1 and a response of 'No' as 0. A total score was calculated for each paper included (Appendix S2) and a score of 13–14 was graded 'High-Quality', 11–12 was 'Moderate-Quality', and <11 was 'Poor Quality'. Similarly, when using the NOS assessment, we used the system suggested by Herzog et al. in 2013.[18]

The following data from all selected articles were extracted: year, country, geographic location, ethnicity of population, crude prevalence of HPV infection with 95% confidence intervals, mean age of study cohort and most common HPV type reported (Table 1). The clinical and laboratory equipment involved in HPV diagnosis included medical records, screening tests, blood tests, clinical examinations, cervical Pap smears, oral gargles, penile swabs, tampons, saliva samples and polymerase chain reaction.

2.4 | Statistical analysis

A random-effects model was used to calculate prevalence and their associated 95% confidence intervals. Heterogeneity between the studies was evaluated by I^2 statistics, with $I^2 > 50\%$ indicating significant heterogeneity (Figure 2). To address the high heterogeneity, a subgroup analysis was performed on the basis of continent (Africa/Asian-Oceanic/American), type of study (case-control/cohort/cross-sectional), study quality (high/moderate/low) and sample size (less or more than 500; Table 2). Meta-regression was performed to further explore the heterogeneity caused by geographical location, type of study, sample size and study quality (Appendix S3). Statistical analyses were conducted using STATA 15, with P-values <0.05 considered to denote differences that were statistically significant.

3 | RESULTS

3.1 | Study and patient characteristics

A total of 1,377 articles on HPV infection in Indigenous populations were identified from PubMed, Scopus, EMBASE and Web of Science. Four hundred and fourteen articles were included after removing duplicate records, two hundred and twenty-one records were excluded after reviewing titles, and one hundred and fifteen

TABLE 1 Characteristics of all the studies included reporting the prevalence of HPV in Indigenous populations

Author	Publication year	Indigenous identity	Geographical location	Country
Lee NR et al.	2019	American Indian	Great Plains, (North Dakota, South Dakota, Nebraska and Iowa), USA	USA
Ghosh S et al.	2019	Koraga, Marathi Naika and Malekudiya	Udupi south-coastal Karnataka, India	India
Vargas-Robles D et al.	2018	Piaroa Amerindian	Venezuelan Amazonas State in the Orinoco River basin, South America	South America
Nascimento M et al.	2018	Quilombola	Maranhão, Brazil, South America	South America
McGregor S et al.	2018	Indigenous	Australia	Australia
Fuenmayor A et al.	2018	Eñepa Indigenous	Maniapure, Bolivar State, Venezuela, South America	South America
Camara HB et al.	2018	Fula, Mandinka, Wollof, Jola, Serere	The Gambia, Africa	Africa
Awua AK et al.	2017	Ghanian indigenous	Akuse, Ghana, West Africa	Africa
Gauthier B et al.	2016	Inuit Tribe	Nunavik, Quebec, Canada	Canada
Sharma K et al	2015	Gond, Korku, Munda, Lohra, Asur, Oreo, Muria, Halba, Abhujmaria	Madhya Pradesh, Jharkhand and Chhattisgarh in India	India
Mongelos P et al.	2015	Maka´, Nivacle´, Sanapana´, South Enxet, Toba-Qom.	Paraguay, South America	South America
Fonseca AJ et al.	2015	Yanomami, Macuxi, Wapishana	northern Amazonian region	South America
Bennet R et al.	2015	Inuit	Nunavik, Quebec, Canada	Canada
Severini A. et al.	2013	Metis, Inuit and First Nations people	Labrador, Canada	Canada
Schabath MB et al.	2013	Pacific Islander Men	Southern Florida in USA, S–ao Paulo in Brazil, or Cuernavaca in Mexico	USA and South America
Metcalfe S et al.	2013	Inuit	Nunavik, northern Quebec	Canada
Mendoza L et al.	2013	Maká, Nivaclé, Sanapaná, Enxet Sur, Toba-Qom	Paraguay, South America	South America
Jiang Y et al.	2013	First Nations	Northern Canada, Yukon	Canada
Jiang Y et al.	2013	First Nations, Metis and Inuit	Nunavut, Labrador, Yukon in Northern Canada	Canada
Rumbold AR et al.	2012	Indigenous Arnhem Land people	Arnhem Land region, Australia	Australia
Deluca GD et al.	2012	Pilagá community	Formosa, Argentina	South America
Blas MM et al.	2012	Shipibo-Konibo	Lima and Ucayali, Peruvian Amazon	South America
Akogbe GO. et al.	2012	Asian/Pacific Islanders	Sao Paulo, Brazil; the state of Morelos, Mexico; or metropolitan Tampa, Florida, United States	USA and South America
Parvez R et al	2012	Nicobarese Tribe	Andaman Nicobar Islands, India	India

Prevalence %	N	Sex distribution	AGE	Most prevalent HPV type	Type of Study	Quality of study	
						NIH Scale	Newcastle Ottawa scale
34.8 (31.3–38.4)	698	Female: 698 Male: 0	27–48 years	HPV 51 (7.6%)	Cross-sectional	Moderate	High
40.6 (37.8–43.5)	1140	Female:1140 Male: 0	Mean – 40 years	HPV 18 (28.3%)	Cross-sectional	High	High
70.1 (58.6–80.6)	67	Female: 67 Male: 0	12–53 years	HPV 18 (45%)	Cross-sectional	High	High
12.6 (9.3–15.8)	395	Female: 395 Male: 0	12– 84 years	HPV 68 (26%)	Cross-sectional	High	Moderate
58.1 (38.2–88)	155	Female:155 Male: 0	18–26 years	HPV 16 (17.4%)	Cross-sectional	High	High
45.71 (29.4–62.5)	35	Female: 35 Male: 0	13–67 years	–	Cross-sectional	High	Moderate
12.1 (8.2–16.6)	232	Female: 232 Male: 0	20 –49 years	HPV 52 (17.8%)	Cross-sectional	High	High
67.3 (61–73.2)	226	Female: 226 Male: 0	15–65 years	–	Cross-sectional	High	High
22.68 (19.6–26)	657	Female: 657 Male: 0	15–69 years	HPV 16 (9.13%)	Cohort	High	High
12.9 (11.4–14.4)	2034	Female: 2034 Male: 0	9–25 years	HPV 16 (54%)	Cross-sectional	High	High
22.7 (19.6–26)	181	Female: 181 Male: 0	Mean – 30 years	HPV 16 (4.4%)	Cross-sectional	High	Moderate
39.6 (35.9–43.4)	664	Female: 664 Male: 0	Mean – 35.8 years	HPV31 (8.7%)	Cross-sectional	High	High
39.9 (35.2–44.7)	416	Female: 416 Male: 0	15–69 years	HPV 16 (25.32%)	Cohort	High	High
21.4 (19.3–23.6)	1370	Female: 1370 Male: 0	13 – 86 years	HPV 16 (32.2%)	Cross-sectional	High	Moderate
25.2 (17.5–33.8)	111	Female: 0 Male: 111	18–70 years	–	cohort	High	High
47.62 (43.5–51.8)	548	Female: 548 Male: 0	15–69 years	–	Cohort	High	High
23.2 (17.3–29.7)	181	Female: 181 Male: 0	Mean – 30 years	HR HPV (16.1%)	Cross-sectional	High	High
24.3 (19.4–29.5)	276	Female: 276 Male: 0	14 years and above	HPV 16 (10.6%)	Cross-sectional	High	High
27.6 (26.7–28.6)	8446	Female: 8446 Male: 0	18–69 years	HPV 16/18 (7.5%)	Cross-sectional	High	High
63.9 (59.7–68)	521	Female: 521 Male: 0	18–60 years	HPV 16 (5.8%)	Cross-sectional	High	Moderate
46.7 (40.2–53.2)	227	Female: 227 Male: 0	Mean – 30 years	HPV–16 (19.4%)	Cross-sectional	High	Moderate
31.5 (28.9–34)	1253	Female: 1253 Male: 0	15–39 years	HPV 16 (10.8%)	Case-control	High	High
42.2 (33.3–51.7)	111	Female: 0 Male: 111	18–70 years	HPV 16/18 (18.9%)	Cohort	High	High
2.3 (0–9.7)	43	Female: 43 Male: 0	20–60 years	HPV 16 (100%)	Cross-sectional	High	High

(Continues)

TABLE 1 (Continued)

Author	Publication year	Indigenous identity	Geographical location	Country
Schmidt-Grimminger D C et al	2011	American Indian	Northern Plains (South Dakota) in USA	USA
Garland SM et al.	2011	Aboriginal and Tores strait islander	Australia	Australia
Camargo M et al.	2011	Leticia-Amazonas, Chaparral- Tolima, Engativa-Bogota, Girardot-Cundinamarca, Tumaco-Narino	Colombia, South America	South America
Bell MC et al.	2011	American Indian	Northern Plains, South Dakota, USA	USA
Alfonsi GA et al	2011	American Indian/Alaska Native	Boston, Baltimore, New Orleans, Seattle, Denver, Los Angeles	USA
Hamlin-Douglas, et al.	2010	Inuit women	Nunavik, Northern Quebec Canada	Canada
Giuliano AR et al.	2009	Asian and Pacific islander American Indian/Alaska native	US, Brazil, Mexico	USA and South America
Wall SR et al.	2005	Wolof, Mandinka, Fula	Gambia, West Africa	Africa
Tonon, SA et al.	2004	Guarani Indian tribe	Rain forest of Misiones, north-eastern Argentina South America	South America
Brito EB et al.	2002	Parakana Tribe, Amerindian	Brazilian Amazonia	South America
Schiff M et al	2000	South-western Tribe, American Indian	Albuquerque, New Mexico, USA.	USA and South America
Marais D et al.	2000	Bushmen/ San tribe	Schmidtsdrift, Southern Africa	Africa
Bowden FJ et al.	1998	Aboriginal	'Top End' of the Northern Territory	Australia
Young T et al.	1997	Aboriginal	Canada	Canada
Davidson M et al.	1994	Alaska Native (Eskimo, Aleut, Indian)	Alaska	USA
Becker TM et al.	1991	Pueblo and Navajo, Native American	Albuquerque, New Mexico, South America	South America
Bloch B et al.	1988	Himba, Herero, Bushman, Barakwena and the Vasquella, Ovambo, Damara, Angolan, coloured, Nama, Xhosa and Kavango	South west Africa/ Namibia	Africa

Note: – indicates not mentioned in article.

were excluded after reviewing the abstracts. According to the inclusion and exclusion criteria, 41 studies were included in the meta-analysis after reading full texts of 78 records. The flowchart is listed in Figure 1.

In the final analysis, we included 2 case-control studies, 5 cohort studies and 34 cross-sectional studies; after stratifying on the basis of sample size, we found 24 studies to have included less than 500 individuals in their research and 17 had a sample above 500. On the basis of geographical location, 5 studies involved African Indigenous populations, 7 studies involved Asian and Oceanic (Australia, New Zealand) Indigenous populations, and 29 studies involved American Indigenous populations. The characteristics of these studies are summarized in Table 1. Also, we found only 3 studies which had data on males and other sites of infection (apart from cervical) like oropharynx, penile and anal; and since it is such a small number, it was insufficient to stratify the studies on the basis of sex and site.

3.2 | Study quality

Results of the study quality for the included records are listed in Supplement Table 1. One study was considered low quality, 7

Prevalence %	N	Sex distribution	AGE	Most prevalent HPV type	Type of Study	Quality of study	
						NIH Scale	Newcastle Ottawa scale
41.7 (35.5–48.1)	235	Female: 235 Male: 0	18–65 years	HPV 18 (–)	Cross-sectional	High	High
47.5 (43.6–51.3)	655	Female: 655 Male: 0	17–40 years	HPV 16 (9.4%)	Cross-sectional	High	High
63.8 (49.5–77.1)	47	Female: 47 Male: 0	14–69 years	HPV 16 (–)	Cross-sectional	High	High
46.8 (40–53.7)	205	Female: 205 Male: 0	16–65 years	–	Cross-sectional	High	High
32.6 (27.4–38.2)	291	Female: 291 Male: 0	18–65 years	–	Cross-sectional	High	Moderate
28.9 (25.2–32.7)	554	Female: 554 Male: 0	15–69 years	–	Cross-sectional	High	Moderate
50 (34.8–65.2)	22 20	Female: 0 Male: 42	18–70 years	–	Cross-sectional	High	Moderate
24.3 (20.2–28.6)	699	Female: 699 Male: 0	15–54 years	HPV 16 (19%)	Cross-sectional	Moderate	High
63.8 (57.1–70.2)	207	Female: 207 Male: 0	12–64 years	HPV16 (30.8%)	Cross-sectional	Moderate	Low
14.3 (5.1–26.7)	42	Female: 42 Male: 0	10–73 years	HPV 16 (4.7%)	Cross-sectional	High	Moderate
42.46 (37.6–46.9)	438	Female: 438 Male: 0	18–45 years	HPV 31 (8.4%)	Case-control	High	High
56.96 (50.7–63.1)	244	Female: 173 Male: 71	Up till 83 years	HPV 45	Cross-sectional	Moderate	High
41.8 (36.7–46.9)	359	Female: 359 Male: 0	Mean - 26.1 years	HPV 16 (19.2%)	Cross-sectional	Moderate	High
33.6 (29.6–37.7)	530	Female: 530 Male: 0	–	HPV 18 (14.7%)	Cross-sectional	Moderate	Moderate
21 (18.6–23.4)	1126	Female: 1126 Male: 0	14–79 years	HPV 16 (–)	Cross-sectional	Moderate	High
6.4 (4.8–8.3)	746	Female: 746 Male: 0		HPV31, 33, 35 (46.9%)	Cross-sectional	Low	Moderate
24.4 (21.3–27.7)	684	Female: 684 Male: 0	>20–45 years<	–	Cross-sectional	High	Moderate

studies were of moderate quality, and 35 studies were of high quality according to the NIH scale. According to the Newcastle-Ottawa scale, 4 studies were of low quality, 13 of moderate quality, and 26 studies were of high quality.

3.3 | Pooled prevalence of HPV infection in Indigenous populations

The prevalence of HPV infection in Indigenous populations in the included studies ranged from 2.3 percent to 70.1 percent. We were unable to stratify the prevalence proportion on the basis of sex and site due to insufficient data in each; hence, we report a pooled overall prevalence. The pooled prevalence was 34.2% (95% CI: 28.9%–39.8%) with a high level of heterogeneity between studies (I^2 = 98.7, p < 0.0001) (Figure 2). The prevalence of HPV infection in Indigenous populations of Africa, America and Asia/Oceania was similar: 33% (95% CI: 12.8%–57.1%), 33% (95% CI: 27.4%–38.9%) and 33% (95% CI: 17.5%–51.3%), respectively. The prevalence in studies with more than 500 individuals was 29.4% (95% CI: 28.9%–39.8%) and in studies with less than 500 individuals was 36.3% (95% CI: 28.7%–44.4%). On the basis of type of studies, the pooled prevalence of cohort studies was 35.3%

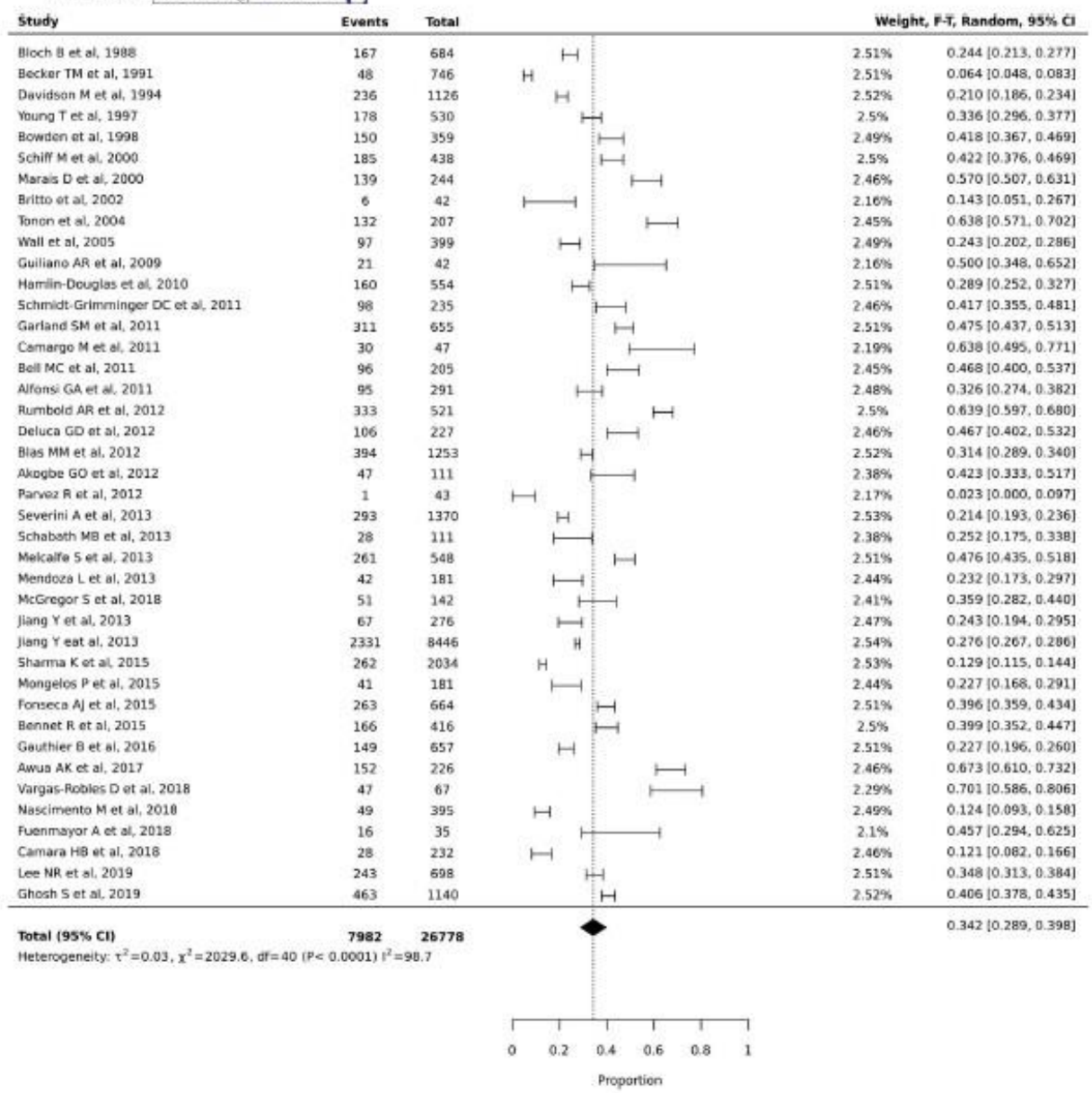


FIGURE 2 Forest plot of prevalence reported by all 41 studies included in the systematic review

(95% CI: 25.7%–45.5%), for case-control studies was 36.7% (95% CI 26.4%–47.7%) and for cross-sectional studies was 31.6% (95% CI: 25.2%–38.3%).

3.4 | Meta-regression and publication bias

Univariate meta-regression analysis was performed to enable better understanding of the high heterogeneity observed in our meta-analysis (Figure 2). The results showed that study population, age, study period, study quality, diagnostic criteria and study design could not explain the high heterogeneity between studies (Table 2) ($p > 0.50$).

The most prevalent type of HPV seen was HPV 16, seen as most common type in 21 studies out of 41 (51.2%); second most common type seen was HPV 18 in 4 studies (9.7%). Eight studies did not mention the most prevalent HPV type seen, 3 studies declared HPV 31 as the most commonly detected, and a single study each showed HPV 45, 51, 52 and 68 as most prevalent type seen.

4 | DISCUSSION

The current systematic review and meta-analysis demonstrate a pooled prevalence of 34.2% of HPV infection in Indigenous

TABLE 2 Subgroup analysis about incidence of HPV in indigenous populations in different categories

Subgroup category	Number of studies	Prevalence rate	95% Confidence intervals	I^2 (%)
Total	41	34.2	28.9–39.8	98.7
Geographical Location				
African Indigenous populations	5	33	12.8–57.1	99.2
American Indigenous populations	29	33	27.4–38.9	98.4
Asian-Oceanic populations	7	33.3	17.5–51.3	99.3
Type of study				
Cohort	5	35.3	25.7–45.5	94.5
Case-control	2	36.7	26.4–47.7	94
Cross-sectional	32	31.6	25.2–38.3	99
Number of participants				
<500	24	36.3	28.7–44.4	96.8
More than 500	17	29.4	22.6–36.8	99.2
Quality of study				
NIH Scale				
High	33	33.7	27.9–39.7	98.7
Moderate	7	36.9	23.7–51.2	98.7
Newcastle-Ottawa Scale				
High	24	34.4	27.4–41.7	98.9
Moderate	13	29.1	20.2–38.8	98.1

populations at a global level. The pooled prevalence in Indigenous populations of Asia and Oceania, Africa and America was all similar (33%).

Our major finding was a strikingly high pooled prevalence in Indigenous populations, as compared to a previously reported HPV prevalence in general populations.[6,7] It has been suggested that health conditions of Indigenous people are over-represented among the poor and disadvantaged, especially in developed countries.[15] The Centre of Disease Control (CDC) in the United States released data which suggest that native communities carry an increased burden of infectious disease especially sexually transmitted diseases.[3] It has been reported[17,19] that the prevalence of high-risk HPV related to invasive cervical cancer was 32.7% in American Indian/Alaskan Native populations in the United States compared with 24.9% in the non-Indigenous populations. A crude incidence of HPV-related cervical cancer in 9 Indigenous populations of the Brazilian Amazon was 46/100 000, which indicated a public health concern, also suggesting a weakness in the current secondary prevention programme.[20] A systematic review evaluating the prevalence of HPV infection in women of the general population in 5 continents reported a 24% prevalence in African region, 16.1% in the American regions and 14% in the Asian regions.[21] Our systematic review has delineated the specific prevalence of HPV infection in Indigenous populations of similar regions, and our findings show a consistently higher incidence of the infection in all the regions. Similarly, another systematic review evaluating the HPV infection in Middle East and North Africa found a prevalence of 16% in the general population of these regions compared with the 33% prevalence we found Indigenous populations of the African regions.[22]

It is important to consider the unique genetic makeup and race-specific characteristics of Indigenous populations. It has been suggested that there may be disparities in immune regulating cells (human leucocyte antigen, immunoglobulin-like receptors) including germ line variations, which affects the mechanisms of defending and destroying these infections, which could lead to fluctuations in frequency across populations.[23,24] A study of 3 specific tribes (Aymara, Mestizo and Quechua) of Bolivian Andean women has revealed an unexpected number of cases infected with HPV-31, and it was suggested that this could again be attributed to the specific immunogenicities of different ethnicities.[23,25] Another possible genetic link has been suggested which states that there is a possibility of this group of people to be less resistant to tumour development.[26]

Indigenous people are deeply spiritual and have strong beliefs regarding life principles; many of those beliefs may impact on health-related behaviours. For example, in New Zealand, Maori women are fearful of cervical screening procedures as they feel that it is tapu (taboo to something sacred) and incorporates whakama (embarrassment and shyness).[27] In 2018, a study found a significant association between female genital mutilating practices and the persistence of HPV infection or cervical cancer in the Fula ethnic population in Gambia.[28] Another social practice of marrying girls at a very young age to middle-aged men and starting conception of children immediately after menarche was observed in the Parakana tribe of the Brazilian Amazonian region. These girls were having children every 2–3 years and the practices of bigamy and multiple sexual partners are common, making the females extremely susceptible to HPV infections (prevalence of 43%) and subsequent cervical

cancer.[29,30] Similar trends were observed among American Indian women, where high carriage of HPV infection was associated with 2–5 sexual partners, sexual practices without condoms, first sexual experience between 11 and 18 years of age and more than 3 pregnancies.[31] Number of sexual partners was an important predictor of HPV infection in the Métis population of Canada.[32] The younger age of onset of sexual practices and less likely use of condoms have been observed in Maori tribes also.[33] The Enepa tribe from Venezuela have deep-rooted belief systems and monogamous customs, which includes the marriage of sexually mature girls at an early age (13–15 years) and the male dominant role in the family. Health promotion and education strategies do not appear to have been successful.[34] A Pilaga community in Northern Argentina showed very high prevalence of HPV infection (46.7%).[35] Several reasons for not attending cervical cancer screening were described by Canadian Inuit women, including previous painful experiences and embarrassment to be examined by a male nurse.[32] Nahua, Mam and Huichol women in rural Mexico said that reasons to avoid any treatment included travel cost and time, and if the villages had their own health centre, they also feared the outcome or result. The inability of the doctor/diagnostician to speak the local language made communication difficult, with the women given paperwork without an explanation which increased confusion. There was a reported shortage of disposable speculums in the local centres which created unhygienic impressions in the minds of the women.[36]

Indigenous populations are often socially disadvantaged and find frequent clinic visits, especially for those living in rural or remote locations, for screening to be an unnecessary expense (in countries where health care is not free).[27,37]

There may be a lack of awareness of this sexually transmitted infection, its prevention and vaccine effectiveness among some Indigenous groups. The lack of a healthy relationship between health workers and these communities has been observed.[27] In Maniapure of Venezuela, over one third of the study population (36.7%) had an HPV infection.[33] Only one in ten women understood the concept of sexually transmitted infections and less than half were aware of different contraceptive methods.[30] Fuenmayor and colleagues[34] suggested that these findings highlight the immense gap of knowledge and awareness among this population and recommended the need for more population-specific targeted health strategies.[34] Vasilevska and colleagues[38] observed that although early cervical cancer incidence was less among Indigenous women of Australia, Canada, United States and New Zealand as compared to the general population, the incidence of invasive cancer at later stages with increased mortality was much higher. This suggests there are many barriers to early detection and treatment for these high-risk populations.[38] There were many discrepancies noted between carriage of high-risk HPV infection and other HPV infections in Aboriginal women of Australia, with lack of Pap testing cited as the main reason.[39,40]

There is an observed trend of lower uptake of vaccines by these populations, which may contribute to the spread of infections.[41] Many women from culturally reserved groups may be disinterested in vaccinations due to inaccessibility of vaccination clinics, language barriers and fear of the screening results.[41] The Alaska Indian and Alaska Native population groups have raised concerns regarding the effectiveness and necessity of HPV vaccinations[42,43] especially in their ethnic subgroups, again reinforcing the importance of culturally appropriate and accessible health messages[42] regarding unsafe sexual practices.[44,45] A survey among American Indian physicians revealed that men were less inclined to initiate or complete vaccination schedules and were unaware of the appropriate timing and effectiveness of the vaccine.[45,46] New Zealand is one of the first countries to have achieved higher uptakes and completion of vaccines (56%) in the Indigenous population (Maori).[27] The Los Angeles County health survey showed that 59.3% of Asian/Pacific Islander women were aware of an HPV vaccine and 63.7% showed an eagerness towards getting vaccinated.[46]

Evidence suggests that Indigenous women may be more in favour of self-test kits, where they do not have to experience embarrassment, compromise their body autonomy[27] or seek prior consent from their husbands.[36] Culturally appropriate educational DVDs built in partnership with American Indian Communities are played in the waiting rooms of Local Indian Health Service clinics, hospitals, events, educational institutions, together with posters using American Indian tribal art about HPV infection and vaccine awareness.[46] Inuit women of Quebec (Canada) have developed health promotional activities including announcements on the public radio 3 times a year reminding them of screening tests.[13]

One of the highlights of our review was a high pooled prevalence of HPV infection in Indigenous populations at a global level irrespective of geographical location. A limitation of this review is the heterogeneity of the data included in the meta-analysis.

In conclusion, we can say that Indigenous populations carry an increased burden of HPV infection. The need to address the requirement and vulnerability of these population groups should be a concern and priority for public health policymakers and workers, and also special strategies and steps should be taken to reach out to them by health awareness and promotional groups working globally. The insufficient data on HPV infection of males and different sites apart from cervical show a large gap in the literature and also require the attention of all public health officials and a need to screen and vaccinate the male population of these Indigenous communities as well. Gathering primary data on this subset is of great importance and should be made a research priority.

CONFLICTS OF INTEREST

No conflicts of interest declared.

AUTHOR CONTRIBUTION

Sneha Sethi: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Validation; Writing-original draft; Writing-review & editing. **Anna Ali:** Conceptualization; Methodology; Software; Writing-review & editing. **Xiangqun Ju:** Formal analysis; Investigation; Resources; Software; Supervision; Writing-review & editing. **Annika Antonsson:** Formal analysis; Methodology; Supervision; Writing-review & editing. **RM**

Logan: Conceptualization; Formal analysis; Methodology; Project administration; Validation; Writing-review & editing. **Karen Canfell:** Formal analysis; Investigation; Validation; Writing-review & editing. **Megan Smith:** Formal analysis; Project administration; Writing-review & editing. **Gail Garvey:** Data curation; Project administration; Visualization; Writing-original draft; Writing-review & editing. **Joanne Hedges:** Data curation; Project administration; Supervision; Writing-review & editing. **Lisa Jamieson:** Data curation; Formal analysis; Investigation; Project administration; Supervision; Validation; Writing-review & editing.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/jop.13201.

DATA AVAILABILITY STATEMENT

No additional data available; all data are attached in Supplementary files.

ORCID

Sneha Sethi https://orcid.org/0000-0002-3571-5298

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Ahmedin J. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68:394-424.
2. Office for National Statistics. *Cancer registration statistics, England: first release*, 2016. https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulleins/cancersurvivalinengland/nationalestimatesforpatientsfollowedupto2017 (Accessed September 30, 2019).
3. Lechner M, Breeze CE, O'Mahony JF, Masterson L. Early detection of HPV-associated oropharyngeal cancer. *Lancet*. 2019;393:2123.
4. Koutsky L. The epidemiology behind the HPV vaccine discovery. *Ann Epidemiol*. 2009;19:239-244.
5. Patel C, Brotherton JML, Pilsbury A, et al. The impact of 10 years of human papillomavirus (HPV) vaccination in Australia: what additional disease burden will a nonvalent vaccine prevent? *Euro Surveil*. 2018;23:1700737.
6. Forman D, de Martel C, Lacey CJ, et al. Global burden of human papillomavirus and related diseases. *Vaccine*. 2012;20(30 Suppl 5):F12-23.
7. Bruni L, Diaz M, Barrionuevo-Rosas L, et al. Global estimates of human papillomavirus vaccination coverage by region and income level: a pooled analysis. *Lancet Glob Health*. 2016;4:e453-e463.
8. WHO. Global strategy for elimination of cervical cancer. https://www.who.int/activities/a-global-strategy-for-elimination-of-cervical-cancer
9. Garland SM, Brotherton JML, Condon JR, et al. Human papillomavirus prevalence among indigenous and non-indigenous Australian women prior to a national HPV vaccination program. *BMC Med*. 2011;9:104.
10. Zehbe I, Wakewich P, Wood B, Sameshima P, Banning Y, Little J. Engaging Canadian first nations women in cervical screening through education. *Int J Health Promot Educ*. 2016;54:255-264.
11. Murchland AR, Gottschlich A, Bevilacqua K, et al. HPV self-sampling acceptability in rural and indigenous communities in Guatemala: a cross-sectional study. *BMJ Open*. 2019;9:e029158.
12. Axelsson P, Kukutai T, Kippen R. The field of Indigenous health and the role of colonisation and history. *J Pop Res*. 2016;33:1-7.
13. Paradies Y. Colonisation, racism and indigenous health. *J Pop Res*. 2016;33:83-96.
14. https://www.un.org/development/desa/indigenouspeoples/about-us.html
15. Gracey M, King M. Indigenous Health part 1: determinants and disease patterns. *Lancet*. 2009;374:65-75.
16. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *Int J Surg*. 2010;8:336-341.
17. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336:924-926.
18. Herzog R, Álvarez-Pasquin MJ, Díaz C, Del Barrio JL, Estrada JM, Gil Á. Are healthcare workers' intentions to vaccinate related to their knowledge, beliefs and attitudes? A systematic review. *BMC Pub Health*. 2013;13:154.
19. Craig Rushing S, Stephens D, Shegog R, et al. Healthy native youth: improving access to effective, culturally-relevant sexual health curricula. *Front Public Health*. 2018;6:225.
20. Balbinotto G, Jardim A. Epidemiology and economic impact of cervical cancer in the state of Romania (Brazilian Amazonic Region): the perspective of the Brazilian unified health system. *Int J Gynaec Obs*. 2012;119(S3):O0082-O0083.
21. Bruni L, Diaz M, Casteesague X, Ferrer E, Bosch X, de Sanjose S. Cervical human papillomavirus prevalence in 5 continents: Meta-analysis of 1 million women with normal cytological findings. *J Infec Dis*. 2010;202:1789-1799.
22. Obeid DA, Almatrrouk SA, Alfageeh MB, Al-Ahdal MA, Alhamlan FS. Human papillomavirus epidemiology in populations with normal or abnormal cervical cytology or cervical cancer in the middle-east and North Africa: A systematic review and meta-analysis. *J Infec Pub Health*. 2020;13:1304-1313.
23. Guinan KJ, Cunningham RT, Meenagh A, et al. Signatures of natural selection and coevolution between killer cell immunoglobulin-like receptors (KIR) and HLA class I genes. *Genes Immun*. 2010;11:467-478.
24. Akogbe GO, Ajidahun A, Sirak B, et al. Race and prevalence of human papillomavirus infection among men residing in Brazil, Mexico and the United States. *Int J Cancer*. 2012;131:E282-E291.
25. Cervantes J, Lema C, Hurtado L, et al. Prevalence of human papillomavirus infection in rural villages of the Bolivian Amazon. *Rev Inst Med Trop São Paulo*. 2003;45:131-135.
26. Frisch M, Biggar RJ, Goedert JJ. Human papillomavirus-associated cancers in patients with human immunodeficiency virus infection and acquired immunodeficiency syndrome. *J Natl Cancer Inst*. 2000;92:1500-1510.
27. Adcock A, Cram F, Lawton B. Acceptability of self-taken vaginal HPV sample for cervical screening among an under-screened Indigenous population. *Aust N Z J Obstet Gynaecol*. 2019;59:301-307.
28. Camara HB, Anyanwu M, Wright E, Kimmit PT. Human Papillomavirus genotype distribution and risk factor analysis amongst reproductive age women in urban Gambia. *J Med Microbiol*. 2018;67:1645-1654.
29. Brito EB, Martins SJ, Menezes RC. Human Papillomaviruses in Amerindian women from Brazilian Amazonia. *Epidemiol Infec*. 2002;128:485-489.
30. Brito EB, Silva ID, Stávale JN. Amerindian women of the Brazilian Amazon and STD. *Eur J Gynaecol Oncol*. 2006;27:279-281.
31. Bell MC, Schmidt-Grimminger D, Jacobsen C, Chauhan SC, Maher DM, Buchwald DS. Risk factors for HPV infection among American Indian and white women in the Northern Plains. *Gynecol Oncol*. 2011;121:532-536.
32. Demers A, Shearer B, Totten S, et al. P1-S2.69 prevalence of HPV infections in metis and first nations living in Manitoba, Canada. *Sex Transm Infect*. 2011;87(Suppl 1):A152.

33. Blakely T, Kvizhinadze G, Karvonen T, Pearson AL, Smith M, Wilson N. Cost-effectiveness and equity impacts of three HPV vaccination programmes for school-aged girls in New Zealand. *Vaccine*. 2014;32:2645-2656.
34. Fuenmayor A, Fernández C, Pérez V, et al. Detection of precancerous lesions in the cervix and HPV infection in women in the region of Maniapure, Bolivar State. *Ecancermedicalscience*. 2018;12:884.
35. Deluca GD, Basiletti J, Schelover E, et al. Chlamydia trachomatis as a probable cofactor in human papillomavirus infection in aboriginal women from north-eastern Argentina. *The Braz J Infec Dis*. 2011;15:567-572.
36. Allen-Leigh B, Uribe-Zúñiga P, León-Maldonado L, et al. Barriers to HPV self-sampling and cytology among low-income indigenous women in rural areas of a middle-income setting: a qualitative study. *BMC Cancer*. 2017;17:734.
37. Schiff M, Becker TM, Masuk M, et al. Risk factors for cervical intraepithelial neoplasia in southwestern American Indian women. *Am J Epidemiol*. 2000;152:716-726.
38. Vasilevska M, Ross SA, Gesink D, Fisman DN. Relative risk of cervical cancer in indigenous women in Australia, Canada, New Zealand, and the United States: A systematic review and meta-analysis. *J Public Health Pol*. 2012;33:148-164.
39. Bowden F, Tabrizi S, Paterson B, Garland S, Fairley C. Determination of genital human papillomavirus genotypes in women in Northern Australia using a novel, self-administered tampon technique. *Int J Gynecol Cancer*. 1998;8:471-475.
40. Cordon JR, Armstrong BK, Barnes T, Zhao Y. Cancer incidence and survival for Indigenous Australians in the Northern Territory. *Aus NZ J Public Health*. 2007;29:123-128.
41. Anomie MA, Amaranti T, Burns J, Burrow S, Drew N, Elwell M, et al. (2017). Overview of Australian Aboriginal and Torres Strait Islander health status 2016. http://www.healthinfonet.ecu.edu.au/health-facts/overviews
42. Alfonsi GA, Datta SD, Mickiewicz T, et al. Prevalence of high-risk HPV types and abnormal cervical cytology in American Indian/Alaska Native women, 2003–2005. *Public Health Rep*. 2011;126:330-337.
43. Buchwald D, Muller C, Bell M, Schmidt-Grimminger D. Attitudes toward HPV vaccination among rural American Indian women and urban White women in the northern plains. *Health Educ Behav*. 2013;40:704-711.
44. Olshen E, Woods ER, Austin B, Luskin M, Bauchner H. Parental acceptance of the human papillomavirus vaccine. *J Adolescent Health*. 2005;37:248-251.
45. Toffolon-Weiss M, Hagan K, Leston J, Peterson L, Provost E, Hennessy T. Alaska Native parental attitudes on cervical cancer, HPV and the HPV vaccine. *Int J Circumpol Health*. 2008;67:363-373.
46. Dela Cruz MRI, Tsark JAU, Chen JJ, Albright CL, Braun KL. Human Papillomavirus (HPV) vaccination motivators, barriers, and brochure preferences among parents in multicultural Hawai'i: a qualitative study. *J Canc Educ*. 2017;32:613-621.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Sethi S, Ali A, Ju X, et al. A systematic review and meta-analysis of the prevalence of human papillomavirus infection in Indigenous populations – A Global Picture. *J Oral Pathol Med*. 2021;00:1-12. https://doi.org/10.1111/jop.13201

End of Published Paper

5.6 SUPPLEMENTARY FILES

5.6.1 : Quality assessment using National Institute of Health (NIH) Scale for the cross-sectional and cohort studies included in the systematic review.

	Study and year	Search question or objective in this paper clearly stated	Study population clearly specified and defined	Participation rate of eligible persons at least 50%	Subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants	Sample size justification, power description, or variance and effect estimates provided	For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured	Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed	Exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable	Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants	Was the exposure(s) assessed more than once over time	Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants	Were the outcome assessors blinded to the exposure status of participants	Was loss to follow-up after baseline 20% or less	Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome	Score	Grade
	Cross-sectional studies and cohort																
1.	Bloch et al, 1988	Yes	Yes	Yes	Yes	No	NA	NA	NA	NA	NA	Yes	NA	NA	No	12	Moderate
2.	Kijser et al 1988	Yes	Yes	Yes	Yes	No	NA	NA	NA	NA	NA	Yes	NA	NA	Yes	13	High
3.	Becker et al, 1991	Yes	Yes	Yes	Yes	No	NA	NA	NA	NA	NA	No	NA	NA	Yes	10	Low
4.	Kijser et al 1993	Yes	Yes	Yes	Yes	No	NA	NA	NA	NA	NA	Yes	NA	NA	Yes	13	High
5.	Davidson et al, 1994	Yes	Yes	Yes	Yes	No	NA	NA	NA	NA	NA	Yes	NA	NA	No	12	Moderate
6.	Young et al 1997	Yes	Yes	Yes	No	No	NA	NA	NA	NA	NA	Yes	NA	NA	Yes	12	Moderate
7.	Bowden et al, 1998	Yes	Yes	Yes	No	No	NA	NA	NA	NA	NA	Yes	NA	NA	No	11	Moderate
8.	Marsis et al 2000	Yes	Yes	Yes	No	No	NA	NA	NA	NA	NA	Yes	NA	NA	Yes	12	Moderate
9.	Brito et al, 2002	Yes	Yes	Yes	Yes	No	NA	NA	NA	NA	NA	Yes	NA	NA	Yes	13	High
10.	Tonn et al 2004	Yes	Yes	Yes	Yes	No	NA	NA	NA	NA	NA	Yes	NA	NA	No	12	Moderate
11.	Wall et al 2005	Yes	Yes	Yes	No	No	NA	NA	NA	NA	NA	Yes	NA	NA	Yes	12	Moderate
12.	Hamlin-Douglas et al, 2008	Yes	Yes	Yes	Yes	No	NA	NA	NA	NA	NA	Yes	NA	NA	Yes	13	High
13.	Giuliano AR et al, 2009	Yes	Yes	Yes	Yes	No	NA	NA	NA	NA	NA	Yes	NA	NA	Yes	13	High
14.	Camargo et al, 2010	Yes	Yes	Yes	Yes	Yes	NA	NA	NA	NA	NA	Yes	NA	NA	Yes	14	High
15.	Bell et al, 2011	Yes	Yes	Yes	Yes	No	NA	NA	NA	NA	NA	Yes	NA	NA	Yes	13	High
16.	Alfonsi et al, 2011	Yes	Yes	Yes	Yes	No	NA	NA	NA	NA	NA	Yes	NA	NA	Yes	13	High
17.	Garland et al, 2011	Yes	Yes	Yes	Yes	Yes	NA	NA	NA	NA	NA	Yes	NA	NA	Yes	14	High
18.	Schmidt-Grimmin et al 2011	Yes	Yes	Yes	Yes	No	NA	NA	NA	NA	NA	Yes	NA	NA	Yes	13	High
19.	Akoghe et al, 2012	Yes	Yes	Yes	Yes	No	NA	NA	NA	NA	NA	Yes	NA	NA	Yes	13	High
20.	Deluca et al, 2012	Yes	Yes	Yes	Yes	No	NA	NA	NA	NA	NA	Yes	NA	NA	Yes	13	High
21.	Parvez et al 2012	Yes	Yes	Yes	Yes	No	NA	NA	NA	NA	NA	Yes	NA	NA	Yes	13	High
22.	Rumbold et al 2012	Yes	Yes	Yes	Yes	Yes	NA	NA	NA	NA	NA	Yes	NA	NA	Yes	14	High
23.	Jiang et al 2013	Yes	Yes	Yes	Yes	No	NA	NA	NA	NA	NA	Yes	NA	NA	Yes	13	High
24.	Jiang et al 2013	Yes	Yes	Yes	Yes	No	NA	NA	NA	NA	NA	Yes	NA	NA	Yes	13	High
25.	Metcalfe et al 2013	Yes	Yes	Yes	Yes	No	NA	NA	NA	NA	NA	Yes	NA	NA	Yes	13	High
26.	Schabath et al 2013	Yes	Yes	Yes	Yes	Yes	NA	NA	NA	NA	NA	Yes	NA	NA	Yes	14	High
27.	Severini et al 2013	Yes	Yes	Yes	Yes	No	NA	NA	NA	NA	NA	Yes	NA	NA	Yes	13	High

28.	Gauthier et al, 2015	Yes	Yes	Yes	Yes	No	NA	NA	NA	NA	NA	Yes	NA	NA	Yes	13	High
29.	Fonseca et al, 2015	Yes	Yes	Yes	Yes	Yes	NA	NA	NA	NA	NA	Yes	NA	NA	Yes	14	High
30.	Bennet et al, 2015	Yes	Yes	Yes	Yes	No	NA	NA	NA	NA	NA	Yes	NA	NA	Yes	13	High
31.	Mongelos et al 2015	Yes	Yes	Yes	Yes	No	NA	NA	NA	NA	NA	Yes	NA	NA	Yes	13	High
32.	Sharma et al 2015	Yes	Yes	Yes	Yes	No	NA	NA	NA	NA	NA	Yes	NA	NA	Yes	13	High
33.	Awua et al, 2017	Yes	Yes	Yes	Yes	Yes	NA	NA	NA	NA	NA	Yes	NA	NA	Yes	14	High
34.	Fuenmayor et al, 2018	Yes	Yes	Yes	Yes	No	NA	NA	NA	NA	NA	Yes	NA	NA	Yes	13	High
35.	Camara et al, 2018	Yes	Yes	Yes	Yes	Yes	NA	NA	NA	NA	NA	Yes	NA	NA	Yes	14	High
36.	McGregor et al 2018	Yes	Yes	Yes	Yes	Yes	NA	NA	NA	NA	NA	Yes	NA	NA	Yes	14	High
37.	Mendoza et al 2018	Yes	Yes	Yes	Yes	Yes	NA	NA	NA	NA	NA	Yes	NA	NA	Yes	14	High
38.	Nascimento et al 2018	Yes	Yes	Yes	Yes	No	NA	NA	NA	NA	NA	Yes	NA	NA	Yes	13	High
39.	Vargas-Robles et al 2018	Yes	Yes	Yes	Yes	No	NA	NA	NA	NA	NA	Yes	NA	NA	Yes	13	High
40.	Ghosh et al 2019	Yes	Yes	Yes	Yes	Yes	NA	NA	NA	NA	NA	Yes	NA	NA	Yes	14	High
41.	Lee et al 2019	Yes	Yes	Yes	Yes	No	NA	NA	NA	NA	NA	Yes	NA	NA	Yes	13	High

5.6.2 : Quality assessment using NIH Scale for the case control studies included in the systematic review

Study and year	Research question or objective clearly stated	Study population clearly specified and defined	Sample size justification	Controls selected or recruited from the same or similar population that gave rise to the cases	Definitions, inclusion and exclusion criteria, algorithms or processes used to identify or select cases and controls valid, reliable, and implemented	Cases clearly defined and differentiated from controls	If less than 100 percent of eligible cases and/or controls were selected for the study, were the cases and/or controls randomly selected from those eligible	Was there use of concurrent controls	Were the investigators able to confirm that the exposure/risk occurred prior to the development of the condition or event that defined a participant as a case	Were the measures of exposure/risk clearly defined, valid, reliable, and implemented consistently (including the same time period) across all study participants	Were the assessors of exposure/risk blinded to the case or control status of participants	Were key potential confounding variables measured and adjusted statistically in the analyses? If matching was used, did the investigators account for matching during study analysis	Score	Grade
	Case control													
Schiff et al 2000	Yes	Yes	Yes	Yes	Yes	Yes	NR	NR	No	Yes	Yes	Yes	11	High
Blas et al, 2012	Yes	Yes	Yes	Yes	Yes	Yes	NR	NR	No	Yes	Yes	Yes	11	High

5.6.3 : Quality assessment using NOS scale (Newcastle Ottawa Scale) for the cohort studies included in the systematic review.

	Selection				Comparability	Outcome			Study Quality
Study	Representativeness of exposed cohort	Selection of the non-exposed cohort	Ascertainment of the exposure	Demonstration that the outcome was not present at the start of the study	Based on design and analysis	Assessment of outcome	Follow up long enough for outcomes to occur	Adequacy of the follow up cohort	Study quality
Schabath et al 2013	*	*	**	*	**	*	*	*	High
Metcalfe et al 2013	*	*	**	*	*	*	*	*	High
Gauthier et al, 2015	*	*	**	*	**	*	*	*	High
Akogbe et al, 2012	*	*	**	*	**	*	*	*	High
Bennet et al, 2015	*	*	**	*	**	*	*	*	High

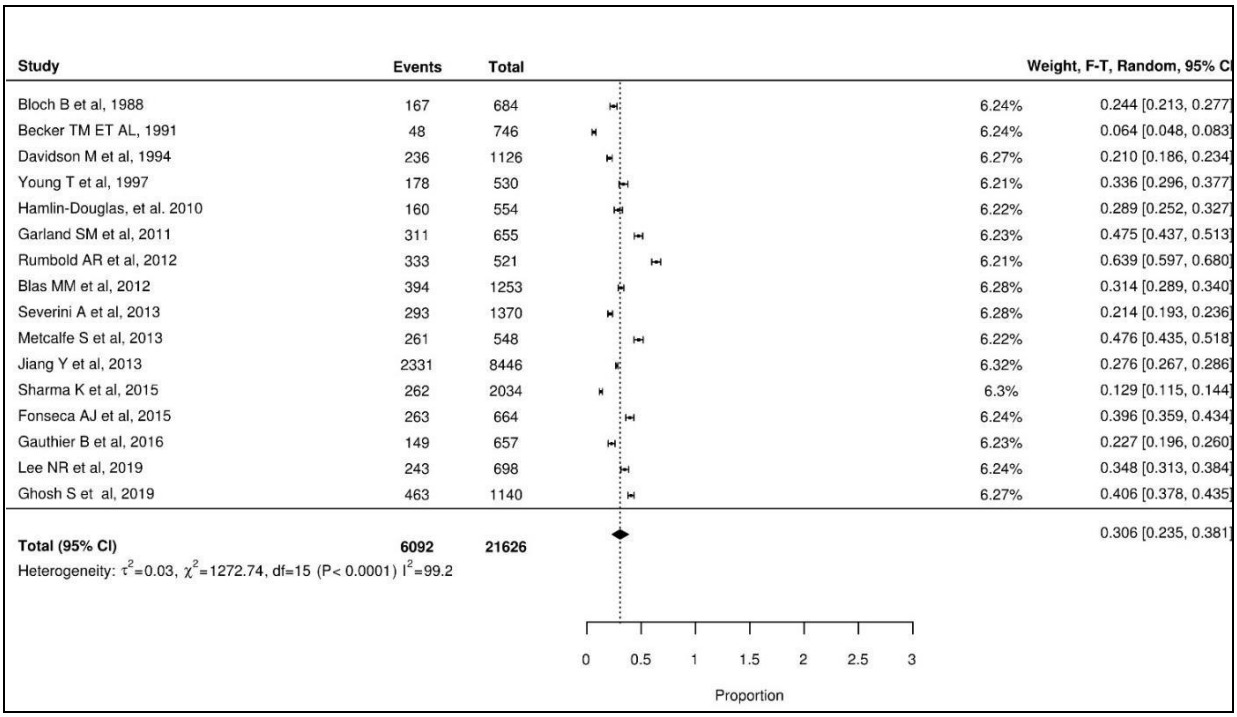
5.6.4 : Quality assessment using NOS scale (Newcastle Ottawa Scale) for the case-control studies included in the systematic review

	Selection				Comparability	Exposure			Study Quality
Study	Is the case definition adequate	Representativeness of the case	Selection of controls	Definition of controls	Based on design and analysis	Ascertainment of exposure	Same method of ascertainment of cases and controls	Non-response rate	Study quality
Schiff et al 2000	*	*	*	*	**	**	*	*	High
Blas et al 2012	*	*	*	*	*	**	*	*	High

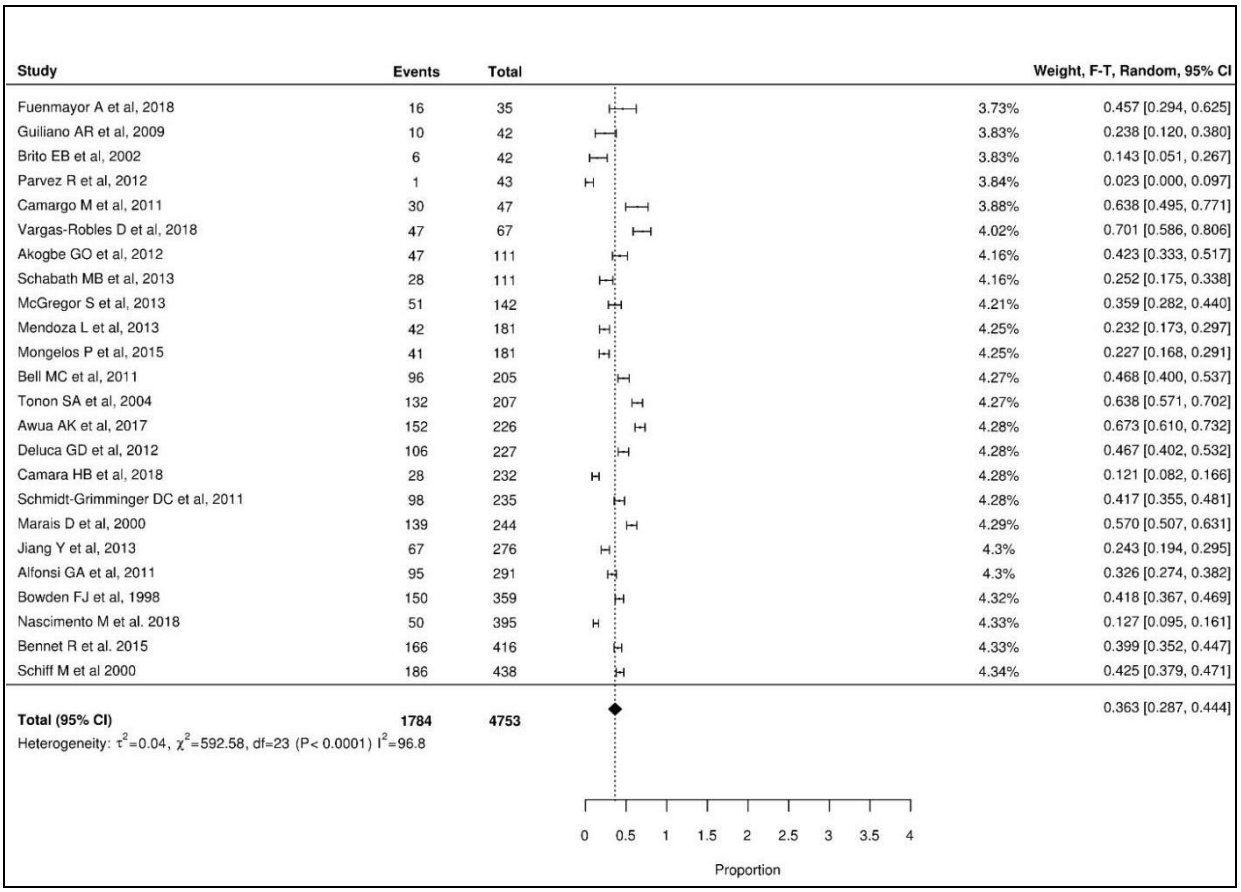
5.6.5 : Quality assessment using NOS scale (Newcastle Ottawa Scale) for the cross-sectional studies included in the systematic review

	Selection				Comparability	Outcome		Study Quality
Study	Representativeness of Sample	Sample Size	Non-respondents	Ascertainment of exposure	Based on design and analysis	Assessment of outcome	Statistical test	Study quality
Young et al, 1997	*	*	*	*	*	**	*	Moderate
Wall et al, 2005	*	*	*	*	**	**	*	High
Vargas-Robles et al, 2018	*	*	*	*	**	***	*	High
Tonon et al, 2004	*	*	*	-	*	*	-	Low
Sharma Et al 2015	*	*	*	**	**	**	*	High
Severini et al, 2013	*	*	*	*	*	**	*	Moderate
Schmidt-Grimminger et al 2011	*	*	*	*	**	***	*	High
Rumbold et al 2012	*	*	*	*	*	**	*	Moderate
Parvez et al 2012	*	*	*	-	*	**	-	Low
Nascimento et al 2018	*	*	*	*	*	**	*	Moderate
Mongelos et al 2015	*	*	-	*	*	**	*	Moderate
Mendoza et al 2018	*	*	*	*	*	***	*	High
McGregor et al 2018	*	*	*	*	*	***	*	High
Marais et al 2000	-	-	*	*	*	**	*	Low
Lee et al 2019	*	*	*	*	*	***	*	High
Kijaer et al 1993	*	*	*	*	*	***	*	High
Kijaer et al 1988	*	*	*	*	*	***	*	High
Jiang et al 2013	*	*	*	*	**	***	*	High
Jiang et al 2013	*	*	*	*	*	***	*	High
Ghosh et al 2019	*	*	*	*	**	***	*	High
Brito et al, 2002	*	*	*	*	*	**	*	Moderate
Fuenmayor et al, 2018	*	*	*	*	*	*	*	Moderate
Bell et al, 2011	*	*	*	*	**	***	*	High
Fonseca et al, 2015	*	*	*	*	**	***	*	High
Deluca et al, 2012	*	*	*	*	*	**	*	Moderate
Alfonsi et al, 2011	*	*	*	*	*	**	*	Moderate
Davidson et al, 1994	*	*	*	*	*	***	*	High
Camara et al, 2018	*	*	*	*	**	***	*	High
Bowden et al, 1998	*	*	*	-	-	**	-	Low
Bloch et al, 1988	*	*	*	*	*	**	-	Moderate
Becker et al, 1991	*	*	*	*	*	**	-	Moderate
Awua et al, 2017	*	*	*	*	**	***	*	High
Camargo et al, 2010	*	*	*	*	**	***	*	High
Giuliano AR et al, 2009	*	*	*	*	*	**	*	Moderate
Garland et al, 2011	*	*	*	*	**	***	*	High
Hamlin-Douglas 2008	*	*	*	*	*	**	*	Moderate

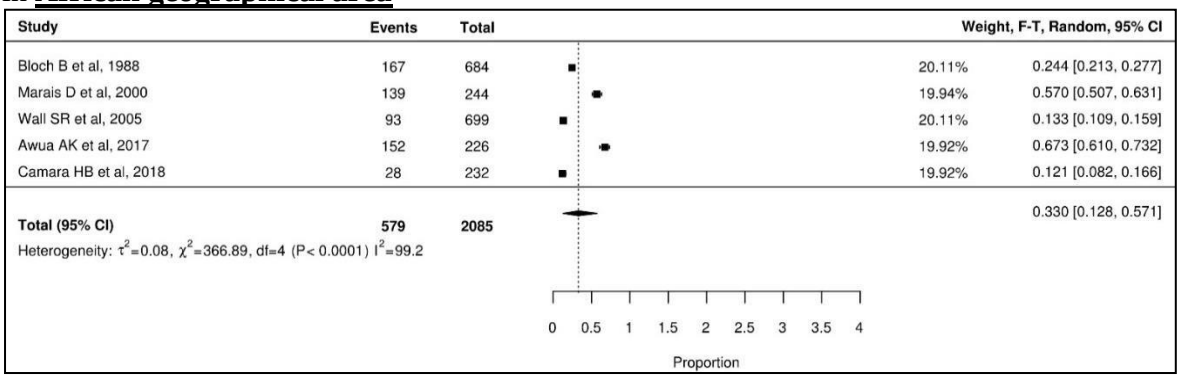
5.6.6 : Forest plot of prevalence of HPV in indigenous populations of included studies with **more than 500 cases**



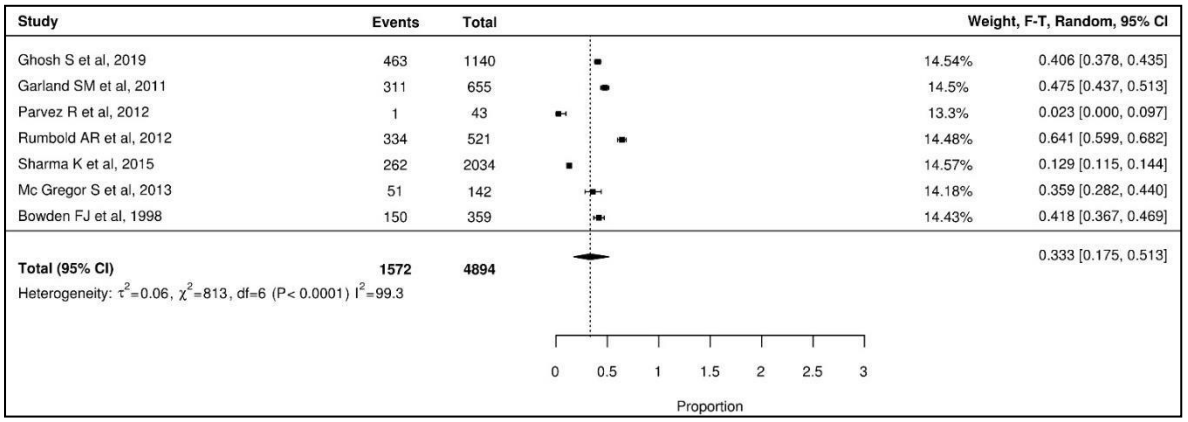
5.6.7 : Forest plot of prevalence of HPV in indigenous populations of included studies with **less than 500 cases**



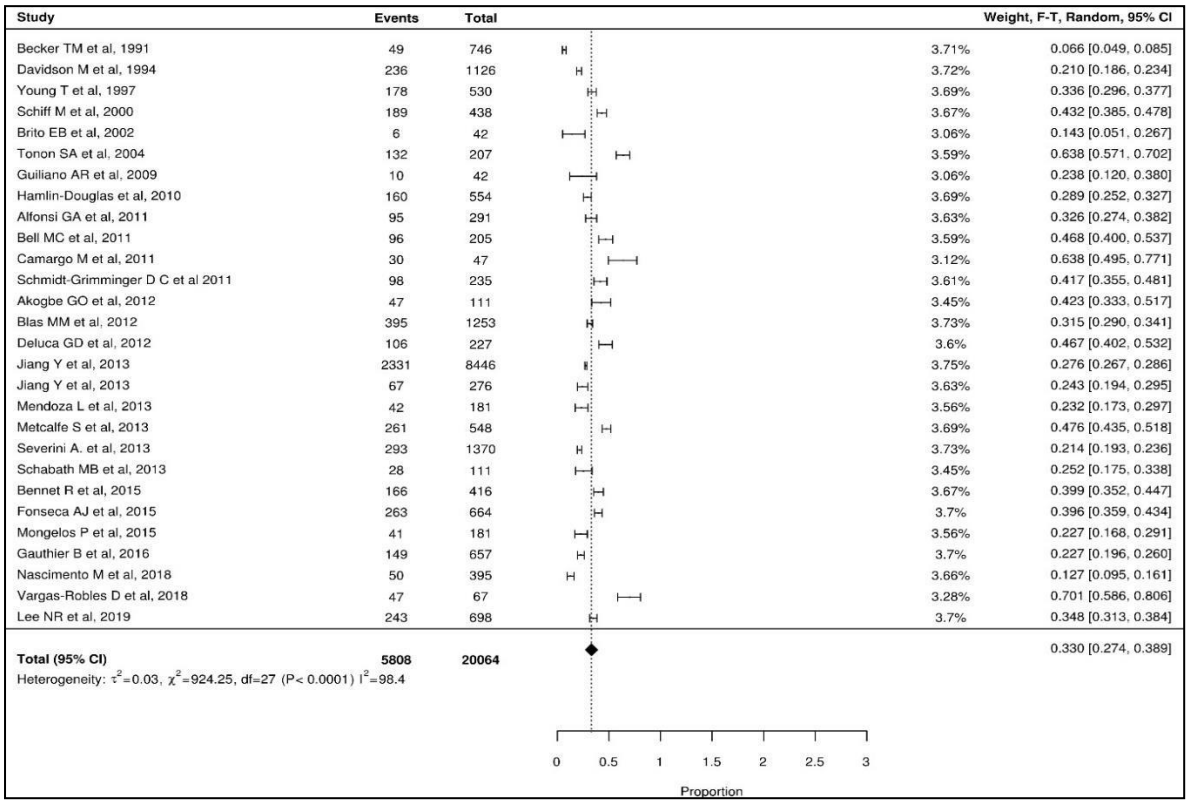
5.6.8 : Forest plot of prevalence of HPV in indigenous populations of included studies based in **African geographical area**



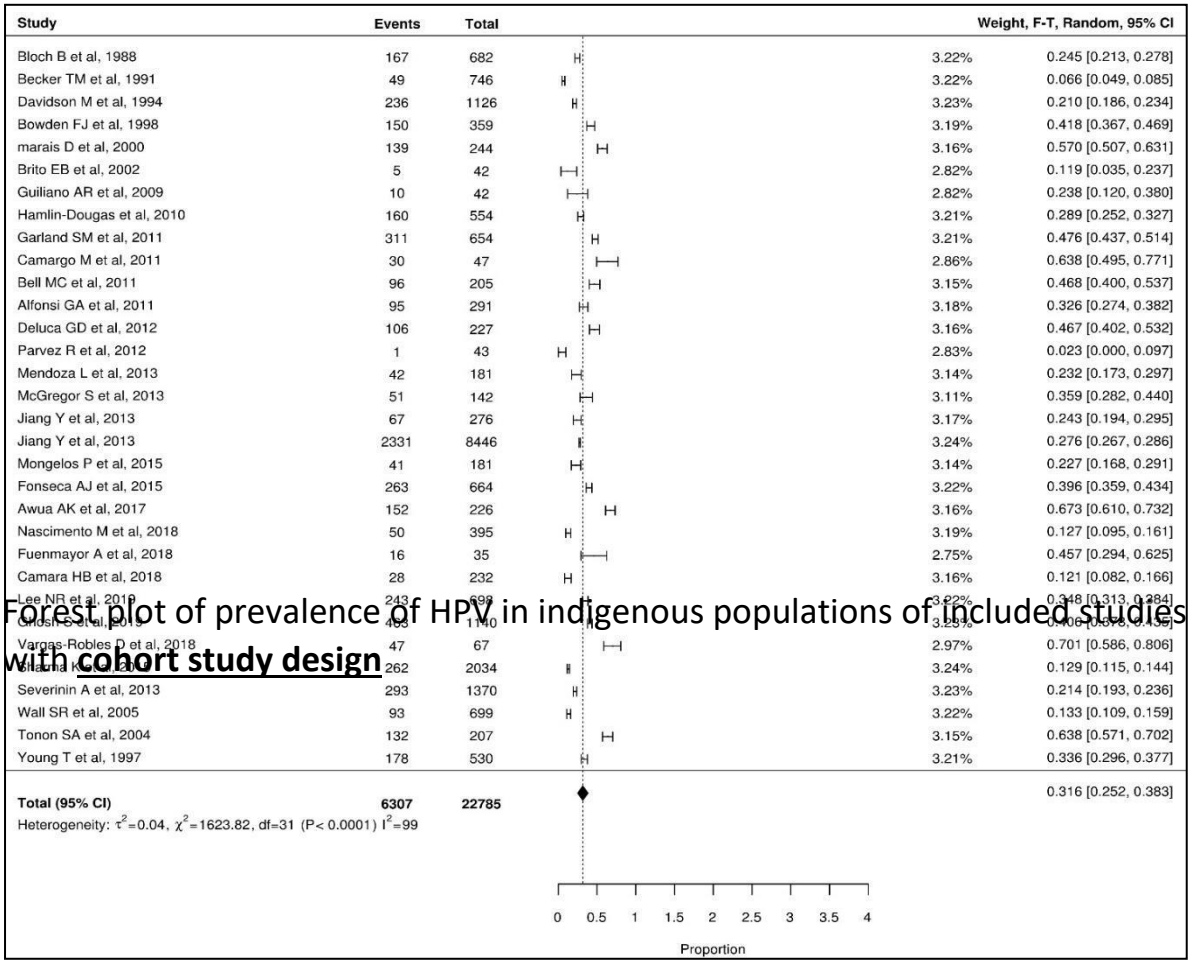
5.6.9 : Forest plot of prevalence of HPV in indigenous populations of included studies based in the **Asian and Oceanic geographical area**



5.6.10 : Forest plot of prevalence of HPV in indigenous populations of included studies based in the **American geographical area**

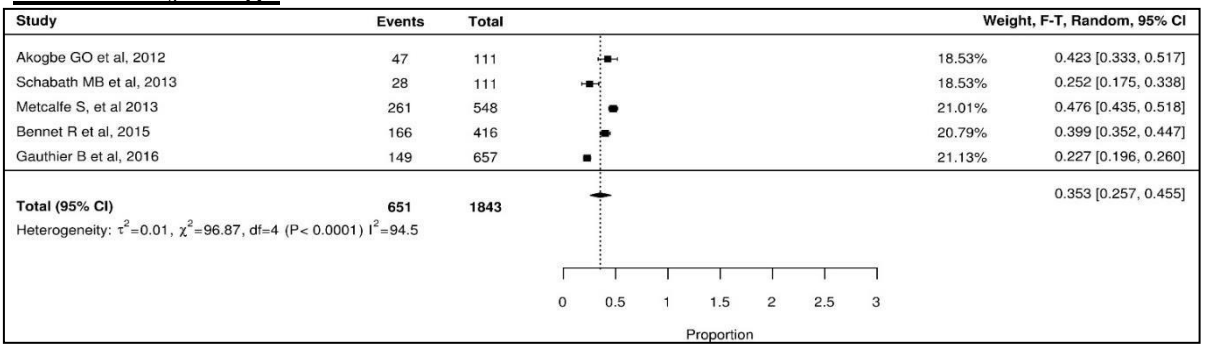


5.6.11 : Forest plot of prevalence of HPV in indigenous populations of included studies with **cross-sectional study design**

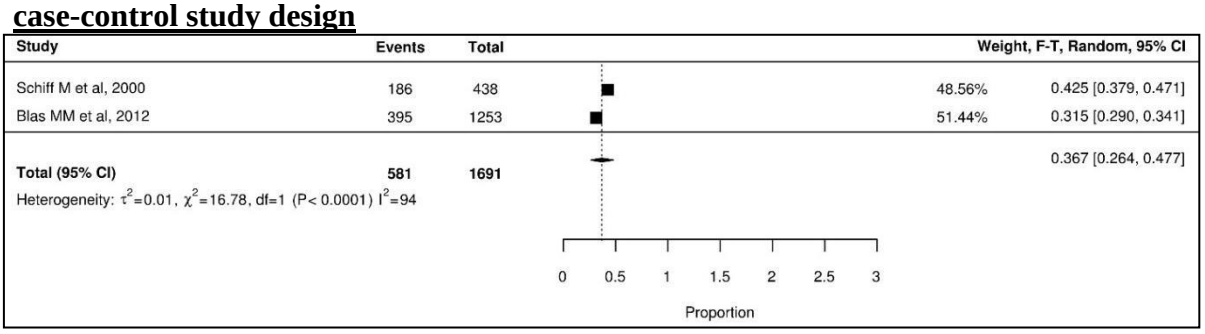


Forest plot of prevalence of HPV in indigenous populations of included studies with **cohort study design**

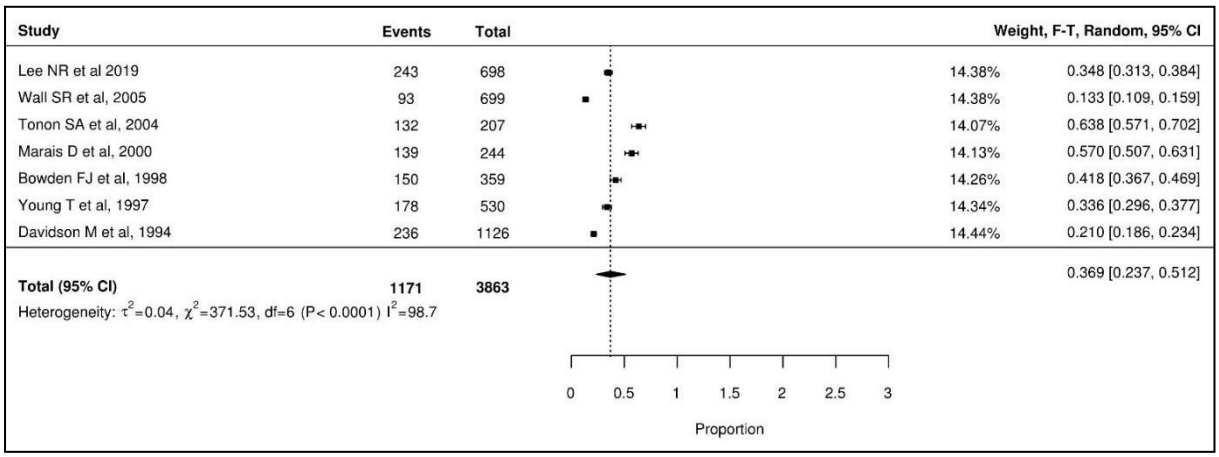
5.6.12 : Forest plot of prevalence of HPV in indigenous populations of included studies with **cohort study design**



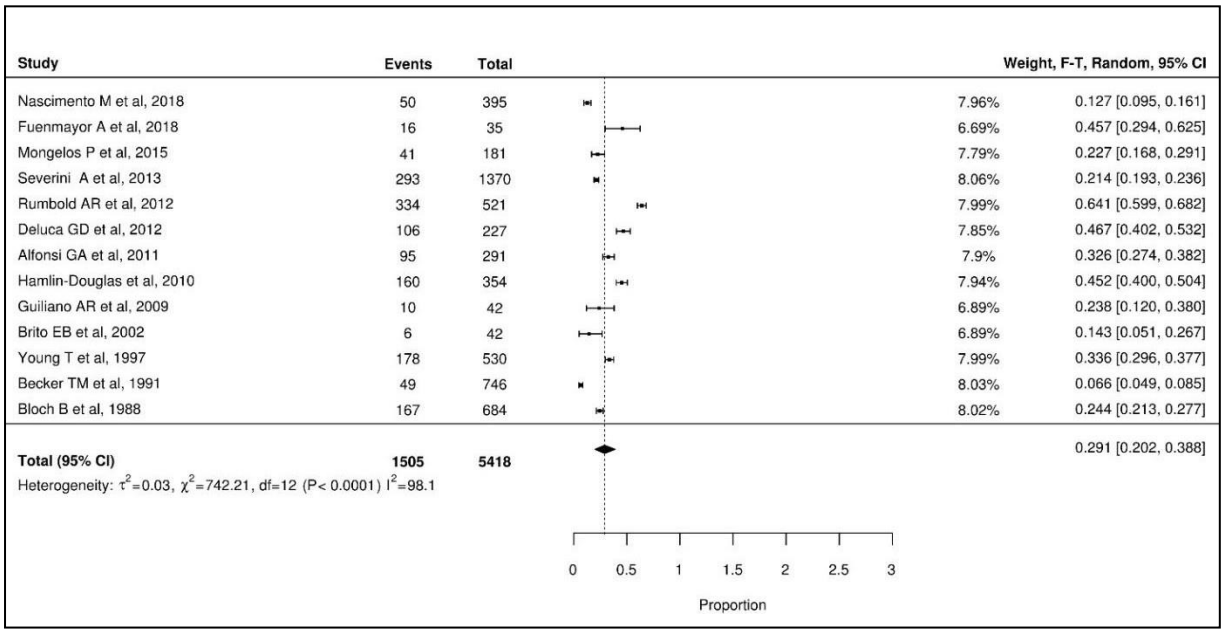
5.6.13 : Forest plot of prevalence of HPV in indigenous populations of included studies with **case-control study design**



5.6.14 : Forest plot of prevalence of HPV in indigenous populations of included studies which are **<u>High quality according to the NIH scale</u>**



5.6.15 : Forest plot of prevalence of HPV in indigenous populations of included studies which are **<u>high quality according to NOS scale</u>**



5.6.15: PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title page – Page 1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Abstract – Page 2,3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Background - Page 4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Background – Page 5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Methods –Page 6, 7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Data sources and Searches in Methods section - page 5 and 6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Data sources and Searches in Methods section - page 5 and 6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Study selection in methods section page 6

Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Data extraction and quality assessment in methods section page 6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Data extraction and quality assessment in methods section second paragraph on page 7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Data extraction and quality assessment in methods section page 6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Prevalence proportion (Results on page 8)
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	(Results on page 8)
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	(Results on page 8)
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Meta-analysis on page 8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Methods section on page 6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Methods section page 7
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Meta-analysis on page 8
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	All forest plots and study data summarised in tables and supplementary files provided

Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Results page 8
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Results page 8
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Meta-analysis page 8
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Discussion second paragraph page 9
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Discussion ending and conclusion page 12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Discussion page 9 and 10
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Declaration page 13

06

Oral HPV infection among Indigenous Australians; incidence, persistence and clearance at 12-months follow-up

6.1 PREFACE AND LINK TO PROJECT

The study (Study 3) presented in this Chapter is the second of three studies in this section that address the second objective of this thesis. The previous Chapter has shown a high pooled prevalence of HPV infection amongst Indigenous Australians, whilst this Chapter focuses on the incidence, persistence and clearance of oral HPV infection over 12-months.

The first step of the HPV-OPC project was to estimate the prevalence of oral HPV infection among Indigenous Australians and to report the prevalence of factors associated with high-risk HPV types (i.e., HPV-16 and HPV-18) and HPV types linked with Heck disease (i.e., HPV-13 and HPV-32). The findings of this step have been published and are attached as Appendix D in this thesis. The next step of this project was to collect the saliva samples at the 12- month follow up and estimate the incidence, persistence and clearance of oral HPV infections. This Chapter elaborates on this stage of the project.

This study is the first to investigate risk factors associated with incidence, persistence and clearance of oral HPV infection amongst an Indigenous population in Australia. This is an original research paper, which analyses the data collected at baseline and 12-months follow up of the larger HPV-OPC study.

6.2 PUBLICATION DETAILS

This paper is under review in the Journal of Cancer Epidemiology, Biomarkers and Prevention as: Sethi S, Ju X, Antonsson A, Canfell K, Smith M, Garvey G, Hedges J, Jamieson L. Oral HPV infection among Indigenous Australians; incidence, persistence and clearance at 12-months follow-up. J Can Epidemiol Biomarkers and Prevention (Under review since August specific date 2021)

6.3 HIGHLIGHTS

- To the best of our knowledge, this is the first prospective, longitudinal cohort study that comprehensively examines and compares the risk factors of incidence, persistence and clearance of oral HPV infection in a large Indigenous Australian population
- The cumulative oral HPV infection incidence was 52.2%.
- Factors associated with persistence and clearance of oral HPV infections included location of residence and unsafe oral sexual behaviours

6.4 STATEMENT OF AUTHORSHIP

Statement of Authorship

Title of Paper	Oral HPV infection among Indigenous Australians; incidence, persistence and clearance at 12-months follow-up
Publication Status	☐ Published ☐ Accepted for Publication ☑ Submitted for Publication ☐ Unpublished and Unsubmitted work written in manuscript style
Publication Details	Sethi S, Ju X, Antonsson A, Canfell K, Smith M, Garvey G, Hedges J and Jamieson L. Oral HPV infection among Indigenous Australians; incidence, persistance and clearance at 12-months follow-up. Cancer Epidemiology, Biomarkers and Prevention (Under Review)

Principal Author

Name of Principal Author (Candidate)	Sneha Sethi		
Contribution to the Paper	Conceiving of Research Question Data Analysis Manuscript writing Editing and Revisions Paper submission for publication Correspondence with Editors in the publication process		
Overall percentage (%)	75%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	15/09/2021

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);
ii. permission is granted for the candidate in include the publication in the thesis; and
iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Xiangqun Ju		
Contribution to the Paper	Orientation on formulation of Research question Revision of Methodology Input in theory application Input in Interpretation of results Revision of Manuscript		
Signature		Date	15/09/2021

Name of Co-Author	Annika Antonsson		
Contribution to the Paper	Revision of Methodology Input in theory application Input in Interpretation of Results Revison of Manuscript		
Signature		Date	15/09/2021

Name of Co-Author	Karen Canfell		
Contribution to the Paper	Revision of Methodology Input in theory application input in Interpretation of Results Revison of Manuscript		
Signature		Date	15/09/2021

Name of Co-Author	Megan Smith		
Contribution to the Paper	Revision of Methodology Input in theory application Input in Interpretation of results Revision of Manuscript		
Signature		Date	17 Sep 2021

Name of Co-Author	Gail Garvey		
Contribution to the Paper	Revision of Methodology Input in theory application input in Interpretation of Results Revison of Manuscript		
Signature		Date	15/09/2021

Name of Co-Author	Joanne Hedges		
Contribution to the Paper	Revision of Methodology Input in theory application Input in Interpretation of results Revision of Manuscript		
Signature		Date	15/09/2021

Name of Co-Author	Lisa Jamieson		
Contribution to the Paper	Orientation on formulation of Research question Revision of Methodology Input in theory application input in Interpretation of Results Revison of Manuscript		
Signature		Date	15/09/2021

6.5 PUBLICATION

Title: Oral HPV infection among Indigenous Australians; incidence, persistence and clearance at 12-months follow-up

Running Title: Oral HPV infection among Indigenous Australians

Sneha Sethi[1*], Xiangqun Ju[1], Annika Antonsson[2], Karen Canfell[3], Megan Smith[3], Gail Garvey[4], Joanne Hedges[1], Lisa Jamieson[1]

1. Australian Research Centre for Population Oral Health, Adelaide Dental School, University of Adelaide, Adelaide, Australia
2. QIMR Berghofer Medical Research Institute, Brisbane, Australia
3. Cancer Council of New South Wales, Sydney, Australia
4. Menzies School of Health Research, Charles Darwin University, Darwin, Australia

Conflicts of Interest: "The authors declare no potential conflicts of interest."

Abstract:

Background: Persistent oral human papillomavirus (HPV) infection is a risk factor for oropharyngeal squamous cell carcinoma (OPSCC). Indigenous Australians have a higher rate of OPSCC than non-Indigenous Australians. Risk factors for oral HPV persistence among Indigenous Australians are poorly understood.

Methods: Participants provided information on socio-demographic characteristics, health-related behaviours including tobacco and alcohol use and sexual history. Participants additionally provided saliva samples for microbial genotyping. Negative log binomial regression models were used to evaluate associations of socio-demographic, health behaviour and sexual behaviour indicators on incident, persistent and cleared oral HPV infection at 12 months follow-up. Estimates were quantified as rate ratios (RR).

Results: Of the 1,011 participants recruited at baseline, 911 provided saliva samples that were β-globin positive (a DNA integrity check), with 321 (35.3%) testing positive for any oral HPV infection. At 12-month follow up, saliva samples were obtained from 743 of the original 1,011 participants (73.5%). Among the 584 participants who provided β-globin positive saliva samples at baseline and 12-month follow-up, 24 (42.6%) had no oral HPV infection at both time points, 130 (22.2%) had new (incident) oral HPV infection at 12 months, 130 (22.2%) had persistent oral HPV infection (i.e. present at both baseline and 12-months), and 75 (12.8%) had oral HPV infection clearance from baseline to 12-months. Rural location of residence, early age of onset of oral sexual behaviours and unsafe (unprotected) oral sexual behaviours were significantly associated with incident and persistent oral HPV infection.

Conclusion: The incidence of oral HPV infection at both baseline and 12-month follow-up was high. Factors associated with persistence and clearance of oral HPV infections included location of residence and unsafe oral sexual behaviours.

Keywords: oral HPV, oropharyngeal squamous cell carcinoma, persistence, clearance, sexual behaviours

Introduction

Human papillomavirus (HPV) infection is one of the most prevalent sexually-transmitted infections in the world, with serious consequences, potentially cancer, associated with its subclinical persistence in the human body. There is sufficient evidence to support the etiological role of this virus in cervical, oropharyngeal, anal and penile precancerous and cancerous lesions (1). There are more than 200 HPV types, with HPV 16 and 18 recognised as having the most severe carcinogenic potential for cervical and oropharyngeal cancer (2).

Although the prognosis for oropharyngeal squamous cell carcinoma (OPSCC) is not favourable, HPV-associated OPSCC has a much better prognosis with recommended "*downstaging*" in the current Tumour-Node-Metastasis (TNM) staging system (3). The TNM Classification is a system for classifying malignancies, primarily used in solid tumours and can be used to assist in prognostic cancer staging. The system has its basis on assessing the tumour, regional lymph nodes, and distant metastasis (4). Due to its unique disease progression and behaviour patterns, HPV-associated OPSCC has now been identified as a distinct disease entity (5). OPSCC has now surpassed cervical cancer as the most common HPV-driven cancer; Oral HPV16 DNA as a screening tool to detect early oropharyngeal squamous cell carcinoma (6).

With an ever-increasing global burden of disease due to oral HPV infections (7, 8), it has become imperative to recognise the significant risk factors which effect incidence, persistence and clearance of oral HPV infection. Although the virus may quickly clear, in some cases it may be retained, leading to increased risk of viral carcinogenesis in certain tissues (9). The natural history of cervical HPV infection and cancer has been extensively reviewed over the past 35 years. It serves as a useful standard and model for comparison with oral HPV infection (10). Improved understanding of oral HPV infection may lead to increased knowledge of the epidemiology and pathogenesis of HPV-associated oral/oropharyngeal cancers. This increased knowledge is crucial for evidence-based management (prevention, screening and treatment) for oral cancer (11).

Although traditional oral cancers are associated with tobacco and alcohol-related behaviours, HPV associated oropharyngeal cancers are associated with sexual behaviours (12). The literature suggests a higher prevalence and incidence of HPV-associated oral cancers among Caucasians, men and younger individuals of higher socioeconomic status (13-16). The recent surge in oral HPV infection-associated cancers can be attributed to the aging of the 'sexual

revolution' cohort of the 1960s, which characteristically show a higher number of sexual partners per individual on average and younger age of onset of sexual activities compared to other age cohorts (12, 17, 18). Demographic variations in sexual behaviours and oral health related behaviours including smoking and tobacco use, explain at least in part the unique epidemiology of both HPV infection and its associated oral and oropharyngeal cancers (15, 19).

Apart from the high-risk HPV types (for example 16 and 18) which could lead to potential malignant lesions, there are some low-risk types which cause papillary or wart like lesions. One of those lesions include, focal epithelial hyperplasia, or Heck disease, which is a comparatively rare benign condition, caused by oral HPV types 13 or 32 (20-23). It was first identified among a Navajo population in the United States (24) and has since been reported among other Indigenous population groups throughout the world.(25, 26)

Indigenous Peoples, as defined by the United Nations (2004), includes all "people with a historical continuity with pre-invasion and pre-colonial societies that developed on their territories, and who consider themselves distinct from other sectors of the societies now prevailing on those territories." A history of colonial settlement in many countries has resulted in environmental dispossession of traditional lands, resources, languages and lore (27-30). Indigenous peoples are over-represented among the poor and underprivileged across the world, and carry a higher burden of preventable health inequalities in comparison to non-Indigenous populations (31). While screening tools and vaccination programs have been successful in reducing overall HPV infection rates, Indigenous communities continue to experience significantly higher infection rates compared to non-Indigenous populations (32-34). In an international study, incidence of cervical cancer was found to be higher among Indigenous women than non-Indigenous women in most countries (Australia, New Zealand, Canada, and the United States) (33). In Australia, there are higher rates of cervical cancer and mortality among Indigenous compared with non-Indigenous women (35).

The main aim of this paper is to describe: (1) acquisition of new oral HPV infections; (2) persistence of existing oral HPV infection and; (3) clearance of oral HPV infection among a cohort of Indigenous Australians across 12 months, and to examine associations with socio-demographic, sexual and health behaviour risk factors among Indigenous Australians. The baseline findings for this study have been published elsewhere (36).

Materials and methods

Participants included 1,011 Indigenous South Australians aged 18+ years taking part in a broader study involving oral HPV infection and OPSCC (11). This study was conducted in partnership with key Indigenous stakeholder groups, and governed by an Indigenous Reference Group. The Indigenous Reference Group was established to provide oversight and cultural guidance on recruitment strategies and data collection. This included Indigenous community members, councillors and health workers, and was chaired by an Indigenous health manager. All components of data collection, including sensitive sexual behaviour questions, were pilot tested and tailored for cultural sensitivity. Baseline data was collected from February 2018 to January 2019 with 12-month follow-up data collected from February 2019 to January 2020. Participants provided a saliva sample at both time points through spitting and dribbling that was collected in a commercially available kit (DNA Genotek Inc), from which microbial DNA was extracted for HPV testing and genotyping. Information on socio-demographic factors, sexual behaviours and health-related behaviours were ascertained by self-report questionnaire, with assistance provided by the study's Senior Indigenous Research Officer (JH) where required.

Ethical approval was received from the University of Adelaide Human Research Ethics Committee and the Aboriginal Health Council of South Australia's Human Research Ethics Committee. All participants provided signed informed consent.

Self-reported Data

A questionnaire with items including demography, income, health behaviours and sexual behaviours was used.

(i) *Sociodemographic characteristics*: Age (dichotomised based on median split at 37 years; 37 and less or 38 and more), sex (male or female), geographic location (metropolitan, i.e. residing in Adelaide, South Australia's capital city and non-metropolitan; i.e. residing elsewhere in the state) and ownership of a government-administered, means-tested health care card.

(ii) *Health and oral health-related behaviours*: Measures included tobacco smoking (currently smoking /formerly smoked or never smoked), alcohol consumption (daily/weekly/monthly, or never) and non-prescription tobacco substitute (i.e., vaporizer or e-cigarette) (former or current /former user or never used)

(iii) *Sexual behaviours*: Included number of people passionately kissed (less than 3 or more than 3), having ever given and received oral sex (yes or no), age of first

giving and receiving oral sex (above 17 years or younger than 16), use of protection when giving and/or receiving oral sex (yes or no), having experienced sexual intercourse (yes or no), age of onset of sexual activity (above 17 years or younger than 16), total number of sexual partners (more or less than 3) and sexual preferences (unisexual or bisexual).

Oral HPV DNA detection and genotyping

Presence of human DNA in saliva samples was confirmed by β-globin polymerase chain reaction (PCR) using the primers PCO3 and PCO4 on all samples in the absence of PCR-inhibiting agents (36). Participants with β-globin–positive saliva samples were included in the data analysis, as β-globin checks the DNA integrity; and any samples with a negative β-globin were considered unusable. A nested PCR system MY09/11 and GP5+/6+ was used for HPV analysis and detection of a large spectrum of mucosal HPV types (36). HPV-positive samples were HPV types by sequencing.

Statistical Analysis

HPV status: The status of oral HPV infection was categorised as no infection at baseline or 12-months, new incident oral HPV infections at 12-months, persistent oral HPV infection at baseline and 12-months and clearance of oral HPV infection at 12-months. Oral HPV types were also categorised on the basis of risk, according to the guidelines specified by the International Agency for Research in Cancer (IARC). HPV types classified as high risk were 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, and 82 (37). Heck's disease was classified as HPV types13 and 32 and the rest were classified as low-risk HPV types.

Basic descriptive analyses were conducted to ascertain frequencies of incident, persistent or cleared oral HPV infections and associated sociodemographic data, health-related behaviours, and sexual history characteristics. The incidence of infection with a given HPV type was calculated exclusively among patients whose first available HPV test result was negative. Persistence defined as the presence of positive oral HPV infection at both baseline and 12-months follow up, Clearance of a prevalent type-specific HPV infection at baseline was considered to have occurred at the first follow-up visit if that infection was no longer detected.

A cumulative oral HPV infection incidence was calculated by calculating the new infection acquired over the 12-month period divided by the number of infection-free cases at baseline.

Rate ratios (RR) of incident oral HPV infection, persistent oral HPV infection and clearance of oral HPV infection were determined using negative log binomial regression modelling. Exposure variables were classified into socio-demographic, health behaviours and sexual health behaviours; variables with associations at the P<0.2 level in bivariate analysis were included in multivariate analysis.

For incident infection and clearance of oral HPV infection at 12 months, four regression models were constructed; Model 1 included socio-demographic indicators, Model 2 included health behaviour indicators, Model 3 included sexual behaviour indicators and Model 4 included socio-demographic, health indicators and sexual behaviours indicators. The final regression model for the acquiring new incident oral HPV infection and clearance of oral HPV infection at 12 months was constructed by adjusting covariates with P-value <0.2 in the bivariate analyses. For persistent oral HPV infection, three regression models were constructed; Model 1 included socio-demographic indicators, Model 2 included sexual behaviour indicators and Model 3 included socio-demographic and sexual behaviours indicators. The final regression model for the persistent oral HPV infection at 12 months was constructed by adjusting covariates with P-value <0.2 in the bivariate analyses.

RRs were considered to be statistically significant when P-values derived from the Wald statistic were =0.05. Data were analysed using STATA version 15.0 (StataCorp). and SPSS (IBM; Version 27).

Results

Recruitment of 1011 participants was completed at baseline, all of whom provided saliva samples and completed questionnaires. Ninety-four baseline saliva samples (9.2%) tested negative for beta globin, and were not included in further analyses. There were no statistically significant differences in sociodemographic characteristics between participants testing positive or negative for beta-globin. The socio-demographic characteristics of this cohort at baseline has been described elsewhere (36, 38). A flow diagram of participants through key study stages is provided in Figure 1.

Of the 911 baseline saliva samples, 321 (35.2%) tested positive for oral HPV infection. We identified 38 HPV types: 3, 6, 7, 10, 13, 16, 18, 30, 31, 32, 33, 34, 35, 39, 40, 42, 44, 45, 51, 52, 53, 54, 56, 58, 59, 62, 66, 67, 68, 69, 72, 73, 81, 82, 84, 87, 90 and 106. The most prevalent HPV types were those associated with Heck's disease; HPV 13 and 32, with a

prevalence of 22.7% (n=207). The data from the baseline findings have been published elsewhere (36).

At 12-month follow up, saliva samples were obtained from 743 of the original 1011 participants, giving a retention rate of 73.5%. After testing for beta globin, 94 (12.6%) tested negative and were not included in subsequent analyses. All samples negative for beta-globin at baseline and 12-months were excluded, yielding a final sample of 584.

Among these 584, 249 (42.6%) participants had no oral HPV infection at baseline and 12-month follow-up, 130 (22.2%) had new oral HPV infections at 12 months, 130 (22.2%) had persistent oral HPV infection (i.e. present at both baseline and 12-months), and 75 (12.8%) had oral HPV clearance from baseline to 12-months. A cumulative oral HPV infection incidence of 52.2%was observed.

High- and low-risk oral HPV infection

There was an increase in the prevalence of HPV 13 and 32 from baseline to 12-month follow-up. Eight new cases of HPV 16 and one new case of HPV 18 were observed from baseline to 12-month follow-up. Among participants with persistent oral infection, just less than half (48%) were positive for HPV 13 or 32. The highest prevalence of oral HPV infection clearance from baseline to 12-month follow-up was observed among participants with HPV 13 or 32 (76.6%). The lowest prevalence was observed among participants with HPV 16 or 18 (18.6%). This information is portrayed in Tables 1 and 2.

The prevalence of oral HPV 13/32 at baseline was 22.7% which increased to 38% at the 12 months follow up. In this study, 79.4% of the new infections at 12 months, 51.4% of the clearance infections, and 64.6% of the persistent infections were positive for HPV 13/32.

Incidence

The sociodemographic characteristics and health related behaviours of participants (n=130) with no HPV infection at baseline and incident oral HPV infection at 12-month follow up are shown in Table 3. Among females, 20.0% belonged to the group of new incident oral HPV infection. Nearly 25% were currently smoking non-tobacco substances. Among participants with a new oral HPV infection at 12-months follow-up, 24.1% reported to have engaged in a sexual relationship after 16 years of age.

Persistence of Infection

The sociodemographic characteristics and health related behaviours of participants who had a persistent oral HPV infection from baseline to the 12-month follow up are described in Table 3. Among the participants of the study residing in regional locations, almost 26% belonged to the group of persistent oral HPV infection. Among this group of participants with persistent oral HPV infection 28.0% reported to have received oral sex.

Clearance of Infection

The sociodemographic characteristics and health related behaviours of participants who had cleared an oral HPV infection from baseline to 12-month follow up are described in Table 3. Among the participants of the study residing in regional locations, almost 17% belonged to the group of clearance of oral HPV infection, and almost 15% had a valid Healthcare card. Of the 548 participants at 12 months follow up, among the group of clearance of infection 15.3% had never received oral sex.

Multivariate modelling

Incidence: In multivariate modelling, sociodemographic indicators significantly associated with incident oral HPV infection at 12 months included healthcare card ownership (Table 4, Model 1). Participants with a health care card were 1.4 times more susceptible of getting a new infection at 12-months. Significant health behaviour indicators in Model 2 included less often to no alcohol consumption and current or former non-tobacco substance use. No-tobacco consumption increased the risk of incidence by 1.6 times. Significant sexual behaviour indicators in Model 3 included lower age of first giving oral sex, never used protection on receiving oral sex and lower age of onset of sexual activity. In Model 4, sexual behaviour indicators that remained significantly associated with new incident infections after adjusting for confounding included lower age of first giving oral sex and never using protection when receiving oral sex.

Persistence: Multivariate modelling for persistent oral HPV infection shows the metropolitan location of residence as a significant socio-demographic indicator (Table 5, Model 1). Participants residing in metropolitan locations were 1.7 times more likely to show persistent oral HPV infection. Significant sexual behaviour indicators in Model 2 included a higher age of first giving oral sex and a lower age of first onset of sexual activity. Participants who stated the age of onset of giving oral sex older than 16 years were 4.3 times more likely to present a persistent Oral HPV infection. In Model 3, sexual behaviour indicators that remained significantly associated with persistent oral HPV infections after adjusting for

confounding included older age of first giving oral sex (4.3 times more likely) and younger age of first onset of sexual activity.

Clearance: In multivariate modelling, socio-demographic indicators significantly associated with clearance of oral HPV infection at 12 months included regional location of residence and no healthcare card status (Table 6, Model 1). Significant health behaviour indicators in Model 2 included alcohol consumption and non-tobacco substance use. No significant sexual behaviour indicators were observed in Model 3 and Model 4.

Discussion

This study provides epidemiologic data on oral HPV infection incidence, persistence and clearance rates in a large cohort of Indigenous South Australians across a follow-up period of 12 months. It also identifies risk factors for incidence, persistence and clearance of oral HPV infection.

The baseline prevalence of oral HPV infection was 15.3 times that reported in a study of young Australians (non-Indigenous) (39). At 12 months follow up, the prevalence increased from 35.2% to 42.1%, which is 8.7 times the estimate reported in a systematic review by Wood et al (40). A longitudinal study (0, 6, 12 and 24 months) of 704 people from Brisbane (18–70 years old) reported an oral HPV prevalence of 10.7% at baseline among the 636 participants who tested positive for β-globin (41).

A higher prevalence of incident oral HPV infection was found among current smokers (64.2%). This is consistent with other reports (13, 16, 42). Investigators have reported that smoking may have an effect on the Langerhans cells, which are involved in instigating an immune response against invading pathogens within the epithelium, leading to a suppressed immune response (13). This smoking induced immunosuppression leads to a high viral load, which has been previously correlated with HPV associated cervical cancer (43-45) and oral diseases including periodontitis (46). An in-vitro study by Alam et al (47) demonstrated the effects of Benzo[*a*]pyrene (a major carcinogen in cigarette smoke) on cervical cells. They observed increased levels of virion synthesis in HPV-infected cell lines. Results with oral mucosal cell lines are not yet available but similar findings and effects can be anticipated.

Previous research has shown that younger age in women is associated with a higher rate of cervical HPV acquisition and clearance, with longer durations of infection in the older groups (48). There is extensive research on HPV associated cervical neoplasia's in women, but due

to limited research on oral HPV in women, there is lack of comparative data to demonstrate the differences in age groups showing persistence and clearance in men and women. Most studies have highlighted the burden of oral HPV infection among men (16). In this study the oral HPV infection rates were higher (at both baseline and 12-month follow up) among women, across both younger and older demographic characteristics. These findings highlight a large gap in the HPV vaccine uptake by Indigenous Australian adolescents, and speaks to an urgent need to ensure high vaccination coverage among all Australians, both Indigenous and non-Indigenous. Although there is little evidence to show the efficacy of the vaccine against specific low risk HPV types (like 13 or 32), there is sufficient indication to demonstrate an effect on decreasing the prevalence of oral HPV infections (49, 50).

The oral carriage of HPV types associated with Heck disease (HPV 13 or 32) in our study were higher than what has been presented in the literature to date (20, 39, 51-55). In this study, the age of participants carrying oral HPV 13/32 was 1.7 times higher (39.8 years) compared to a systematic review (23.1 years) involving 95 studies from other countries (20, 56). Studies have shown that the prevalence of HPV 13 or 32 differs according to residence location (rural or urban) (56) and is common in populations with low annual incomes (26, 58, 59) and overcrowded households (25, 57). The high levels of HPV 13 or 32 may be associated with the Indigenous origin of the population sample in this study, as previous research has established a genetic and ethnic link with Indigeneity and Heck's disease (51, 52, 58-62).

The most important risk indicators observed in this study included location of residence (regional or metropolitan), with an increased persistence observed in participants residing in regional locations and an increased clearance of infections in participants residing in Metropolitan locations. Early onset and unsafe (unprotected) oral sexual behaviours (giving or receiving sex) with were also significant indicators of persistent and new incident oral HPV infections.

This study had several important strengths. To the best of our knowledge, it was the first prospective, longitudinal cohort study that comprehensively examined and compared the risk factors of persistence and clearance of oral HPV infection in a large Indigenous Australian population. The main strength of the study is the engagement of South Australian Indigenous communities which was idealised through partnerships and involvement of the study's Indigenous Reference Group. Over 700 participants were followed up for 12 months.

Previous research has focused on only one or a few HPV types, while our study covered a larger spectrum of high risk and low risk HPV types. A deeper understanding of these epidemiological determinants helps in facilitating public education on early detection of oral HPV infection, and may contribute to the prevention of OPSCC. A comprehensive set of risk factors including sociodemographic variables, lifestyle factors, sexual history, and oral hygiene habits were examined. The findings could inform preventive initiatives and future research for oral HPV infections among Indigenous populations at a global level.

The main limitation is the lack of clinical examinations, anthropometrics and blood samples that would yield important biomarker estimates. The study was not representative, with almost two-thirds of participants being women. Higher oral HPV prevalence was associated with living in rural areas, but people living in these areas were overrepresented in our sample, which may have led to an over-estimation. Some participants were lost to follow-up, meaning the impact on the persistence and clearance rates of oral HPV infection for the whole baseline sample remains unknown. Lastly, lifestyle habits and sexual behaviours were self-reported by study participants, and social desirability bias might have impacted these findings. The 12-month follow-up was delayed and ultimately ceased prematurely due to COVID-19 restrictions.

Conclusion

In this study, the overall prevalence of HPV detected in saliva samples, in a large convenience sample of Indigenous Australians was high, with a significant increase observed after a 12-month follow-up. The most prevalent HPV types were those associated with Heck disease (HPV-13 and HPV-32). Lower age of onset of oral sexual behaviours and decreased use of protection emerged as significant risk predictors for incident oral HPV infection at months. Higher ages of first giving oral sex and lower ages of first sexual experiences were significant risk predictors for persistent oral HPV infection at 12 months. Further funding will be pursued to continue follow-up of this cohort, and to include (after a full medical history) a thorough clinical examination of the external head and neck; a complete oral examination and examination of the oropharynx.

Acknowledgements

The authors gratefully acknowledge the support of the Indigenous Human Papillomavirus and Oropharyngeal Squamous Cell Carcinoma study participants, Indigenous Reference Group,

staff who collected data and key participating Aboriginal Community Controlled Health Organisations.

References

1. Kim SM. Human papilloma virus in oral cancer. J Korean Assoc Oral Maxillofac Surg. 2016;42(6):327-36.
2. Burd EM. Human papillomavirus and cervical cancer. Clin Microbiol Rev. 2003;16(1):1-17.
3. Hoffmann M, Tribius S. HPV and Oropharyngeal Cancer in the Eighth Edition of the TNM Classification: Pitfalls in Practice. Transl Oncol. 2019;12(8):1108-12.
4. Rosen RD, Sapra A. TNM Classification. StatPearls. Treasure Island (FL): StatPearls Publishing

5. Elrefaey S, Massaro MA, Chiocca S, Chiesa F, Ansarin M. HPV in oropharyngeal cancer: the basics to know in clinical practice. Acta Otorhinolaryngol Ital. 2014;34(5):299-309.
6. Tang KD, Vasani S, Menezes L, Taheri T, Walsh LJ, Hughes BGM, et al. Oral HPV16 DNA as a screening tool to detect early oropharyngeal squamous cell carcinoma. Cancer Sci. 2020;111(10):3854-61.
7. Chaturvedi AK, Engels EA, Anderson WF, Gillison ML. Incidence trends for human papillomavirus-related and -unrelated oral squamous cell carcinomas in the United States. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2008;26(4):612-9.
8. Chaturvedi AK, Engels EA, Pfeiffer RM, Hernandez BY, Xiao W, Kim E, et al. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2011;29(32):4294-301.
9. Chen Y, Williams V, Filippova M, Filippov V, Duerksen-Hughes P. Viral carcinogenesis: factors inducing DNA damage and virus integration. Cancers (Basel). 2014;6(4):2155-86.
10. Moscicki A-B, Schiffman M, Burchell A, Albero G, Giuliano AR, Goodman MT, et al. Updating the natural history of human papillomavirus and anogenital cancers. Vaccine. 2012;30 Suppl 5(0 5):F24-F33.
11. Jamieson L, Garvey G, Hedges J, Mitchell A, Dunbar T, Leane C, et al. Human Papillomavirus and Oropharyngeal Cancer Among Indigenous Australians: Protocol for a Prevalence Study of Oral-Related Human Papillomavirus and Cost-Effectiveness of Prevention. JMIR research protocols. 2018;7(6):e10503.

12. Martín-Hernán F, Sánchez-Hernández J-G, Cano J, Campo J, del Romero J. Oral cancer, HPV infection and evidence of sexual transmission. Med Oral Patol Oral Cir Bucal. 2013;18(3):e439-e44.

13. Kero K, Rautava J, Syrjänen K, Willberg J, Grenman S, Syrjänen S. Smoking increases oral HPV persistence among men: 7-year follow-up study. European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology. 2014;33(1):123-33.

14. Chaturvedi AK, Anderson WF, Lortet-Tieulent J, Curado MP, Ferlay J, Franceschi S, et al. Worldwide trends in incidence rates for oral cavity and oropharyngeal cancers. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2013;31(36):4550-9.

15. Osazuwa-Peters N, Adjei Boakye E, Rohde RL, Ganesh RN, Moiyadi AS, Hussaini AS, et al. Understanding of risk factors for the human papillomavirus (HPV) infection based on gender and race. Scientific Reports. 2019;9(1):297.

16. Pierce Campbell CM, Kreimer AR, Lin H-Y, Fulp W, O'Keefe MT, Ingles DJ, et al. Long-term persistence of oral human papillomavirus type 16: the HPV Infection in Men (HIM) study. Cancer Prev Res (Phila). 2015;8(3):190-6.

17. Rettig E, Kiess AP, Fakhry C. The role of sexual behavior in head and neck cancer: implications for prevention and therapy. Expert Rev Anticancer Ther. 2015;15(1):35-49.

18. Brouwer AF, Delinger RL, Eisenberg MC, Campredon LP, Walline HM, Carey TE, et al. HPV vaccination has not increased sexual activity or accelerated sexual debut in a college-aged cohort of men and women. BMC Public Health. 2019;19(1):821.

19. Bosch FX, Lorincz A, Muñoz N, Meijer CJLM, Shah KV. The causal relation between human papillomavirus and cervical cancer. J Clin Pathol. 2002;55(4):244-65.

20. Henke RP, Guèrin-Reverchon I, Milde-Langosch K, Koppang HS, Löning T. In situ detection of human papillomavirus types 13 and 32 in focal epithelial hyperplasia of the oral mucosa. Journal of oral pathology & medicine : official publication of the International Association of Oral Pathologists and the American Academy of Oral Pathology. 1989;18(7):419-21.

21. Jayasooriya PR, Abeyratne S, Ranasinghe AW, Tilakaratne WM. Focal epithelial hyperplasia (Heck's disease): report of two cases with PCR detection of human papillomavirus DNA. Oral diseases. 2004;10(4):240-3.

22. Bassioukas K, Danielides V, Georgiou I, Photos E, Zagorianakou P, Skevas A. Oral focal epithelial hyperplasia. European journal of dermatology : EJD. 2000;10(5):395-7.

23. Ozden B, Gunduz K, Gunhan O, Ozden FO. A Case Report of Focal Epithelial Hyperplasia (Heck's disease) with PCR Detection of Human Papillomavirus. Journal of maxillofacial and oral surgery. 2011;10(4):357-60.

24. Archard HO, Heck JW, Stanley HR. FOCAL EPITHELIAL HYPERPLASIA: AN UNUSUAL ORAL MUCOSAL LESION FOUND IN INDIAN CHILDREN. Oral surgery, oral medicine, and oral pathology. 1965;20:201-12.

25. González-Losa MR, Suarez-Allén RE, Canul-Canche J, Conde-Ferráez L, Eljure-Lopez N. Multifocal epithelial hyperplasia in a community in the Mayan area of Mexico. International Journal of Dermatology. 2011;50(3):304-9.

26. Wu JSA, Florian MC, Rodrigues DA, Tomimori J. Skin diseases in indigenous population: retrospective epidemiological study at Xingu Indigenous Park (XIP) and review of the literature. Int J Dermatol. 2017;56(12):1414-20.

27. Axelsson P, Kukutai T, Kippen R. The field of Indigenous health and the role of colonisation and history. Journal of Population Research. 2016;33(1):1-7.

28. Paradies Y. Colonisation, racism and indigenous health. Journal of Population Research. 2016;33(1):83-96.

29. Richmond CAM, Ross NA. The determinants of First Nation and Inuit health: a critical population health approach. Health & place. 2009;15(2):403-11.

30. Valeggia CR, Snodgrass JJ. Health of Indigenous Peoples. Annual Review of Anthropology. 2015;44(1):117-35.

31. Gracey M, King M. Indigenous health part 1: determinants and disease patterns. Lancet (London, England). 2009;374(9683):65-75.

32. Henderson J, Javanparast, S., MacKean, T., Freeman, T., Baum, F., & Ziersch, A. Commissioning and equity in primary care in Australia: Views from primary health networks. Health and Social Care in the Community,. (2018);26(1):80– 9.

33. Moore SP, Antoni S, Colquhoun A, Healy B, Ellison-Loschmann L, Potter JD, et al. Cancer incidence in indigenous people in Australia, New Zealand, Canada, and the USA: a comparative population-based study. The Lancet Oncology. 2015;16(15):1483-92.

34. Shannon GD, Franco OH, Powles J, Leng Y, Pashayan N. Cervical cancer in Indigenous women: The case of Australia. Maturitas. 2011;70(3):234-45.

35. . AIoHaW. Housing circumstances of Indigenous households:

tenure and overcrowding. Cat no IHW 132 Canberra: AIHW. 2014.

36. Jamieson LM, Antonsson A, Garvey G, Ju X, Smith M, Logan RM, et al. Prevalence of Oral Human Papillomavirus Infection Among Australian Indigenous Adults. JAMA Netw Open. 2020;3(6):e204951-e.

37. Cancer IAfRi. A review of human carcinogens. Part B: biological agents/IARC Working group on the evaluation of carcinogenic risks to humans. Lyon: IARC. 2009.

38. Jamieson LM, Garvey G, Hedges J, Leane C, Hill I, Brown A, et al. Cohort profile: indigenous human papillomavirus and oropharyngeal squamous cell carcinoma study - a prospective longitudinal cohort. BMJ Open. 2021;11(6):e046928.

39. Antonsson A, Cornford M, Perry S, Davis M, Dunne MP, Whiteman DC. Prevalence and risk factors for oral HPV infection in young Australians. PloS one. 2014;9(3):e91761.

40. Wood ZC, Bain CJ, Smith DD, Whiteman DC, Antonsson A. Oral human papillomavirus infection incidence and clearance: a systematic review of the literature. The Journal of general virology. 2017;98(4):519-26.

41. Antonsson A, de Souza M, Wood ZC, Carroll A, Van K, Paterson L, et al. Natural history of oral HPV infection: Longitudinal analyses in prospective cohorts from Australia. International journal of cancer. 2021;148(8):1964-72.

42. Kumar R, Rai AK, Das D, Das R, Kumar RS, Sarma A, et al. Alcohol and Tobacco Increases Risk of High Risk HPV Infection in Head and Neck Cancer Patients: Study from North-East Region of India. PloS one. 2015;10(10):e0140700.

43. Tolstrup J, Munk C, Thomsen BL, Svare E, van den Brule AJ, Grønbaek M, et al. The role of smoking and alcohol intake in the development of high-grade squamous intraepithelial lesions among high-risk HPV-positive women. Acta obstetricia et gynecologica Scandinavica. 2006;85(9):1114-9.

44. Deacon JM, Evans CD, Yule R, Desai M, Binns W, Taylor C, et al. Sexual behaviour and smoking as determinants of cervical HPV infection and of CIN3 among those infected: a case-control study nested within the Manchester cohort. British journal of cancer. 2000;83(11):1565-72.

45. McIntyre-Seltman K, Castle PE, Guido R, Schiffman M, Wheeler CM. Smoking is a risk factor for cervical intraepithelial neoplasia grade 3 among oncogenic human papillomavirus DNA-positive women with equivocal or mildly abnormal cytology. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2005;14(5):1165-70.

46. Labriola A, Needleman I, Moles DR. Systematic review of the effect of smoking on nonsurgical periodontal therapy. Periodontology 2000. 2005;37:124-37.

47. Alam S, Conway MJ, Chen HS, Meyers C. The cigarette smoke carcinogen benzo[a]pyrene enhances human papillomavirus synthesis. Journal of virology. 2008;82(2):1053-8.

48. Castle PE, Schiffman M, Herrero R, Hildesheim A, Rodriguez AC, Bratti MC, et al. A prospective study of age trends in cervical human papillomavirus acquisition and persistence in Guanacaste, Costa Rica. The Journal of infectious diseases. 2005;191(11):1808-16.

49. Schlecht NF, Masika M, Diaz A, Nucci-Sack A, Salandy A, Pickering S, et al. Risk of Oral Human Papillomavirus Infection Among Sexually Active Female Adolescents Receiving the Quadrivalent Vaccine. JAMA Netw Open. 2019;2(10):e1914031-e.

50. Chaturvedi AK, Graubard BI, Broutian T, Pickard RKL, Tong Z-Y, Xiao W, et al. Effect of Prophylactic Human Papillomavirus (HPV) Vaccination on Oral HPV Infections Among Young Adults in the United States. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2018;36(3):262-7.

51. Jarvis A, Gorlin RJ. Focal epithelial hyperplasia in an Eskimo population. Oral surgery, oral medicine, and oral pathology. 1972;33(2):227-8.

52. Axéll T, Hammarström L, Larsson A. Focal epithelial hyperplasia in Sweden. Acta odontologica Scandinavica. 1981;39(4):201-8.

53. Clausen FP, Mogeltoft M, Roed-Petersen B, Pindborg JJ. Focal epithelial hyperplasia of the oral mucosa in a south-west Greenlandic population. Scandinavian journal of dental research. 1970;78(3):287-94.

54. Morency R, Laliberte H, Delamarre R. Focal epithelial hyperplasia of the oral mucosa. The Journal of otolaryngology. 1982;11(1):29-34.

55. Borghelli RF, Stirparo MA, Paroni HC, Barros RE, Dominguez FV. Focal epithelial hyperplasia. Report of five new cases from Argentina. Oral surgery, oral medicine, and oral pathology. 1975;40(1):107-12.

56. Segura Saint-Gerons R, Toro Rojas M, Ceballos Salobreña A, Aparicio Soria JL, Fuentes Vaamonde H. Hiperplasia epitelial focal: Una rara enfermedad en nuestro medio. Medicina Oral, Patología Oral y Cirugía Bucal (Ed impresa). 2005;10:128-31.

57. Carlos R, Sedano HO. Multifocal papilloma virus epithelial hyperplasia. Oral surgery, oral medicine, and oral pathology. 1994;77(6):631-5.

58. Praetorius-Clausen F. Rare oral viral disorders (molluscum contagiosum, localized keratoacanthoma, verrucae, condyloma acuminatum, and focal epithelial hyperplasia). Oral surgery, oral medicine, and oral pathology. 1972;34(4):604-18.

59. García-Corona C, Vega-Memije E, Mosqueda-Taylor A, Yamamoto-Furusho JK, Rodríguez-Carreón AA, Ruiz-Morales JA, et al. Association of HLA-DR4 (DRB1*0404) with human papillomavirus infection in patients with focal epithelial hyperplasia. Archives of dermatology. 2004;140(10):1227-31.

60. Cerón GIA CE, González LMR. . . . Multifocal epithelial hyperplasia : A report of 71 cases. Dermatología Cosmética, Médica y Quirúrgica 2011;9(3):176-80.

61. Spelten B, Grussendorf-Conen EI, Rübben A. Human leukocyte antigen class II alleles and natural history of HPV 2/27/57-induced common warts. Archives of dermatological research. 2004;296(3):105-11.

62. Akoğlu G, Metin A, Ceylan GG, Emre S, Akpolat D, Süngü N. Focal epithelial hyperplasia associated with human papillomavirus 13 and common human leukocyte antigen alleles in a Turkish family. Int J Dermatol. 2015;54(2):174-8.

Table 1: Evolution of oral HPV infection among Indigenous South Australians related to virus oncogenic risk and type of infection from baseline to 12-month follow-up (No infection reported by 249 participants (584-249=335))

HPV type	Total N	Incidence (%, 95% CI)	Persistence (%, 95% CI)	Clearance (%, 95% CI)
Total N	335	130	130	75
Low-risk	33	3.8 (1.6-8.9)	7.4 (3.5-14.8)	20.0 (12.4-30.6)
HPV 13 or 32	235	80.7 (73.0-86.6)	76.5 (66.9-84.0)	48.0 (36.9-59.2)
HPV 16 or 18	30	6.9 (3.6-12.7)	5.3 (2.2-12.1)	18.6 (11.3-29.1)
Other high-risk*	37	8.4 (4.7-14.6)	10.6 (5.8-18.6)	13.3 (7.3-23.0)

Abbreviations: HPV- Human Papillomavirus

*Oral HPV types categorised on the basis of risk, according to the guidelines specified by the International Agency for Research in Cancer (IARC). HPV types classified as other high risk were 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, and 82 (29).

Table 2: Persistence or Clearance of specific High-risk and low-risk (13 and 32) oral HPV infection after 12-month follow up among Indigenous South Australians

HPV types	Total	Incidence N (%)	Persistence N (%)	Clearance N (%)	Changed Type N (%)
HPV 13	77	25 (19.2%)	28 (29.8%)	18 (24%)	6 (16.7%)
HPV 32	158	80 (61.5%)	44 (46.8%)	18 (24%)	16 (44.4%)
HPV 16	19	8 (6.2%)	4 (4.3%)	5 (6.7%)	2 (5.6%)
HPV 18	11	1 (0.8%)	1 (1.1%)	9 (12%)	0 (0%)
HPV 33	2	0 (0%)	0 (0%)	1 (1.3%)	1 (2.8%)
HPV 45	4	1 (0.8%)	2 (2.1%)	0 (0%)	1 (2.8%)
HPV 51	2	0 (0%)	1 (1.1%)	0 (0%)	1 (2.8%)
HPV 52	2	0 (0%)	0 (0%)	2 (2.7%)	0 (0%)
HPV 56	6	4 (3.1%)	1 (1.1%)	1 (1.1%)	0 (0%)
HPV 58	2	0 (0%)	0 (0%)	2 (2.7%)	0 (0%)
HPV 59	2	1 (0.8%)	0 (0%)	1 (1.3%)	0 (0%)
HPV 66	11	4 (3.1%)	4 (4.3%)	1 (1.3%)	2 (5.6%)
HPV 68	1	0 (0%)	0 (0%)	1 (1.3%)	0 (0%)

Abbreviations: HPV- Human Papillomavirus

Table 3: Oral HPV infection among Indigenous Australians related to sociodemographic and behavioural characteristics from baseline to 12-month follow-up

Characteristic	Total (n=584) % (95% CI)	Incidence (n=130) % (95% CI)	p-value	Persistent Infection (n= 130)) % (95% CI)	p-value	Clearance of Infection (n=75) % (95% CI)	p-value
Sex							
Males	30.4 (26.8-34.3)	27.3 (21.3-34.3)	.048*	19.5 (14.3-26.0)	.296	10.0 (6.4-15.4)	.134
Females	69.5 (65.6-73.1)	20.0 (16.3-21)		23.4 (19.5-27.8)		14.3 (11.-18.0)	
Age, y							
37 or less	47.9 (43.9-52.0)	23.5 (18.9-28.9)	.478	20.2 (15.9-25.4)	.279	15.2 (11.4-19.9)	.158
38 or more	52.0 (47.9-56.0)	21.1 (16.8-26.0)		24.0 (19.5-29.1)		11.0 (7.9-15.0)	
Location							
Regional	59.2 (55.2-63.1)	23.3 (19.1-28.0)	.447	25.9 (22.5-30.8)	.010*	10.0 (7.3-12.7)	.011*
Metropolitan	40.7 (36.8-44.7)	20.6 (15.9-26.3)		16.8 (12.6-21.2)		17.2 (13.9-22.6)	
Healthcare Card[a]							
No or Don't Know	27.9 (24.4-31.6)	26.9 (20.7-34.3)	.087	19.6 (14.2-26.4)	.342	7.9 (4.6-11.2)	.024*
Yes	72.0 (68.3-75.5)	20.4 (16.8-24.5)		23.2 (19.4-27.5)		14.9 (13.8-18.7)	
Smoking Status							
Former Smoker or never smoked	44.0 (40.0-48.1)	22.7 (14.8-33.3)	.118	24.0 (15.8-34.6)	.576	17.7 (10.7-27.7)	.891
Current Smoker	56.0 (51.9-60.0)	19.8 (15.8-24.5)		21.4 (17.2-26.1)		12.8 (9.6-16.9)	
Alcohol Consumption							
Daily or weekly or monthly	27.2 (23.7-30.9)	18.2 (13.4-24.1)	.087	23.6 (18.2-29.9)	.557	11.8 (8.0-17.0)	.532
Never	72.7 (69.0-76.2)	24.4 (20.3-28.9)		21.5 (17.6-25.9)		13.6 (10.5-17.4)	
Non-tobacco substance consumption							
Current or former	28.0 (24.5-31.8)	24.9 (21.8-29.4)	.028*	21.8 (18.0-26.2)	.737	11.8 (8.9-15.4)	.228
Never	71.9 (68.1-75.4)	16.9 (12.2-20.8)		23.0 (17.6-29.5)		15.3 (10.9-21.1)	
Number of people passionately kissed on the mouth?							
3 or less	38.8 (34.9-42.8)	23.6 (17.8-30.6)	.602	26.0 (19.9-33.1)	.162	12.4 (8.2-18.3)	.788
More than 3	61.1 (57.1-65.0)	21.6 (17.9-25.9)		20.7 (17.0-24.9)		13.2 (10.3-16.8)	
Ever given oral sex?							
Yes	61.3 (57.2-65.1)	24.7 (19.5-30.8)	.245	25.2 (19.9-31.3)	.172	9.2 (6.1-12.8)	.034*
No	38.6 (34.8-42.7)	20.6 (16.7-25.1)		20.3 (16.5-24.8)		15.3 (13.9-19.4)	
Age of first giving oral sex							
Less than 16 years	14.3 (11.7-17.4)	9.4 (4.7-17.7)	.003*	27.0 (18.6-37.4)	.081	17.6 (10.9-27.2)	.504
More than 16 years	46.9 (42.8-50.9)	24.1 (19.4-29.6)		18.3 (14.1-23.3)		14.6 (10.9-19.3)	
Use of protection on giving oral sex							
Never used protection	41.4 (37.4-45.4)	19.7 (15.2-25.1)	.522	20.9 (16.3-26.4)	.684	14.9 (10.9-19.9)	.727
Used protection sometimes to always	19.8 (16.8-23.3)	22.7 (15.8-31.4)		19.0 (12.7-27.5)		16.3 (10.5-24.5)	
Ever received oral sex?							
Yes	60.2 (56.2-64.1)	23.7 (18.6-29.6)	.495	28.0 (22.8-34.1)	.007*	9.9 (6.6-14.4)	.079
No	39.7 (35.8-43.7)	21.3 (17.3-25.9)		18.4 (14.7-22.6)		15.0 (11.6-19.1)	
Age of first receiving oral sex							
Less than 16 years	16.9 (14.1-20.2)	15.8 (9.9-24.3)	.112	19.8 (13.1-28.7)	.682	16.8 (10.7-25.4)	.555
More than 16 years	43.2 (39.2-47.2)	23.5 (18.6-29.1)		17.9 (13.6-23.1)		14.3 (10.5-19.2)	
Use of protection on receiving oral sex							
Never used protection	45.5 (41.5-49.6)	18.9 (14.6-24.1)	.060	18.5 (14.3-23.7)	.937	16.2 (12.3-21.2)	.263
Used protection sometimes to always	14.7 (12.0-17.8)	28.4 (19.9-38.6)		18.1 (11.4-27.6)		11.3 (6.2-19.8)	
Ever had sex with another person							
Yes	83.9 (80.6-86.6)	27.0 (19.1-36.8)	.228	25.0 (17.3-34.6)	.480	9.3 (4.9-17.0)	.246
No	16.0 (13.3-19.3)	21.3 (17.8-25.1)		21.7 (18.2-25.6)		13.7 (10.9-17.0)	
Age of onset of sexual activity							
Less than 16 years	33.2 (29.5-37.1)	16.6 (12.0-20.5)	.038*	18.6 (13.8-24.7)	.179	16.6 (12.0-22.5)	.119
More than 16 years	50.6 (46.6-54.7)	24.4 (20.8-29.7)		23.7 (19.2-29.0)		11.7 (8.4-15.9)	
Total sexual partners							
3 or less	27.0 (23.5-30.8)	25.7 (19.5-33.1)	.097	24.5 (18.4-31.8)	.304	14.4 (9.7-20.8)	.682
More than 3	56.8 (52.7-60.8)	19.2 (15.2-23.8)		20.0 (16.3-25.1)		13.1 (9.8-17.2)	
Sexual partner preference							
Unisexual (males/females only)	86.6 (83.6-89.1)	22.3 (18.8-26.2)	.896	21.7 (18.3-25.6)	.491	14.0 (11.2-17.3)	.093
Bisexual	13.3 (10.8-16.3)	21.7 (14.4-31.3)		25.0 (17.2-34.8)		7.6 (3.6-15.1)	

Abbreviations: CI – Confidence Intervals, HPV- Human Papillomavirus

[a] Ownership of a government administered health care card is means tested and enables access to services such as publicly funded dental care

*Statistical significance denoted by p<0.0

Table 4: Logistic regression models for new incidence of Oral HPV infection at 12 months among Indigenous Australians

	Model 1 – Socio-demographic (RR, 95%CI), P-value		Model 2 – Health Behaviours (RR, 95%CI), P-value		Model 3 – Sexual Behaviours (RR, 95%CI), P-value		Model 4– Model1+Model 2+Model 3 (RR, 95%CI), P-value	
Socio-demographic								
Sex Males Females	(Reference) 1.4 (0.9-2.2)	.068					(Reference) 1.4 (0.7-2.6)	.287
Healthcare card* No or don't know Yes	(Reference) 1.3 (1.1-2.2)	.031*					(Reference) 1.5 (0.8-2.9)	.178
Health Behaviours								
Smoking habits Never or former Current			(Reference) 1.3 (0.9-2.0)	.115			(Reference) 1.1 (0.6-2.0)	.713
Alcohol consumption Never Daily / weekly/ monthly			(Reference) 0.6(0.4-0.9)	.038*			(Reference) 0.9 (0.5-1.7)	.924
Non-Tobacco Substance consumption Never Current or former			(Reference) 1.6 (1.0-2.6)	.023*			(Reference) 1.1 (0.6-2.0)	.689
Sexual Health Behaviours								
Age of first giving oral sex Less than 16 More than 16					(Reference) 0.2 (0.06-0.6)	0. 007*	(Reference) 0.2 (0.07-0.6)	.010*
Age of first receiving oral sex No Yes					(Reference) 1.4 (0.5-3.9)	0.451	(Reference) 1.2 (0.4-3.4)	.647
Use of protection while receiving oral sex Never Sometimes to always					(Reference) 0.5 (0.2-0.9)	0.041*	(Reference) 0.5 (0.2-0.9)	.035*
Age of onset of sexual activity Less than 16 years More than 16 years					(Reference) 1.0(0.4-2.1)	0. 979	(Reference) 1.0 (0.5-2.3)	.817

Abbreviations: RR –Risk Ratio, CI – Confidence Intervals, HPV- Human Papillomavirus

a Ownership of a government administered health care card is means tested and enables access to services such as publicly funded dental care

*statistical significance denoted by p<0.05

Table 5: Logistic regression models for persistence of Oral HPV infection at baseline and 12-months among Indigenous Australians

	Model 1 – Socio-demographic (RR, 95%CI); P-value		Model 2 – Health Behaviours (RR, 95%CI); P-value		Model 3 – Sexual Behaviours (RR, 95%CI); P-value		Model 4– Model1+Model 2+Model 3 (RR, 95%CI); P-value	
Socio-demographic								
Sex Males Females	(Reference) 0.7 (0.3-1.2)	.194					(Reference) 0.5 (0.2-1.1)	0.094
Age, y 37 or less 38 or more	(Reference) 1.4 (0.8-2.2)	.176					(Reference) 1.6 (0.9-2.7)	0.084
Location Regional Metropolitan	(Reference) 0.4 (0.3-0.8)	.008*					(Reference) 0.5 (0.3-1.0)	0.054
Healthcare card[a] No or don't know Yes	(Reference) 0.4 (0.2-0.9)	.031*					1 (Reference) 0.5 (0.2-1.0)	0.536
Health Behaviours								
Non-tobacco substance consumption Never Current or former			(Reference) 0.7 (0.4-1.2)	.229			(Reference) 0.5 (0.3-1.0)	0.061
Sexual Health Behaviours								
Ever given oral sex No Yes					(Reference) 0.6 (0.2-1.6)	0.381	(Reference) 0.7 (0.2-1.9)	0.502
Ever received oral sex No Yes					(Reference) 0.9 (0.3-2.3)	0.923	(Reference) 1.0 (0.3-2.8)	0.914
Age of first sexual experience Less than 16 More than 16					(Reference) 1.4(0.8-2.5)	0.126	(Reference) 1.4 (0.8-2.5)	0.152
Sexual partner preference Unisexual Bisexual					(Reference) 2.3 (0.5-10.5)	0.233	1 (Reference) 3.8 (0.8-17.6)	0.086

Abbreviations: RR –Risk Ratio, CI – Confidence Intervals, HPV- Human Papillomavirus
*statistical significance denoted by $p<0.05$

Table 6: Logistic regression models for clearance of Oral HPV infection at 12 months among Indigenous Australians

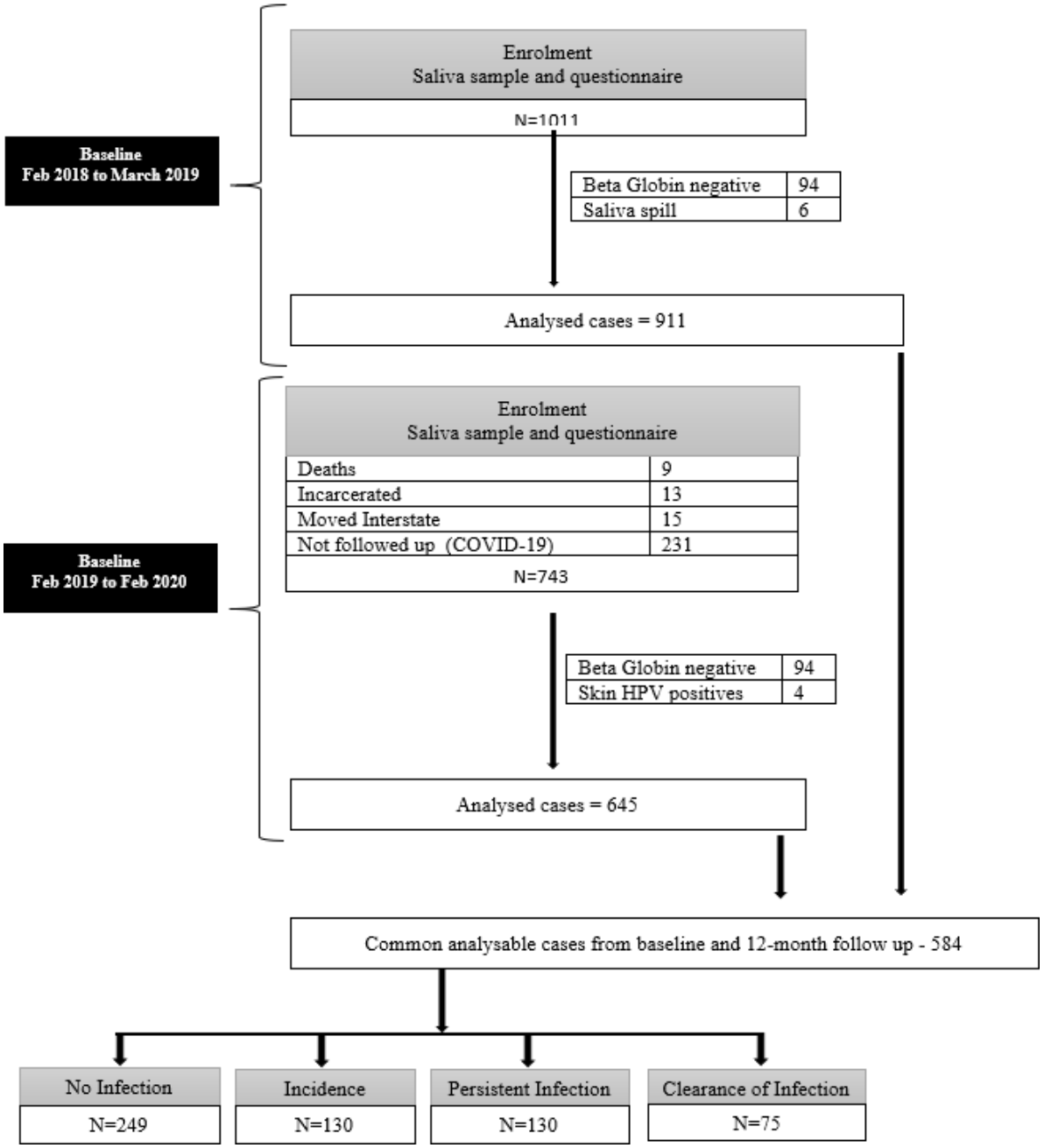
	Model 1 – Socio-demographic (RR, 95%CI); P-value		Model 2 – Sexual Health Behaviours (RR, 95%CI); P-value		Model 3– Model1+Model 2 (RR, 95%CI); P-value	
Socio-demographic						
Location Regional Metropolitan	(Reference) 1.7 (1.1-2.6)	.000*			(Reference) 1.3 (0.7-2.2)	.334
Sexual Health Behaviours						
No of people passionately kissed on mouth Less than 3 More than 3			(Reference) 1.3 (0.6-2.5)	.406	(Reference) 1.2 (0.6-2.4)	0.483
Age of giving oral sex Less than 16 More than 16			(Reference) 4.3 (1.6-11.1)	.002*	(Reference) 4.3(1.7-11.2)	0.002*
Ever received oral sex No Yes			(Reference) 2.1 (0.8-5.0)	.094	(Reference) 2.0 (0.8-4.8)	.104
Age of first sexual intercourse Less than 16 More than 16			(Reference) 0.2 (0.1-0.6)	.004*	(Reference) 0.2 (0.1-0.6)	0.004*

Abbreviations: RR –Risk Ratio, CI – Confidence Intervals, HPV- Human Papillomavirus

[a] Ownership of a government administered health care card is means tested and enables access to services such as publicly funded dental care

[*] statistical significance denoted by $p<0.05$

Figure 1: Flow diagram of participants through key stages of the study (Baseline and 12-months)



End of Paper

07

An update on Heck's disease-A Systematic Review

.1 PREFACE AND LINK TO PROJECT

The study (Study 4) presented in this Chapter is the last of three studies in this section that address the second objective of this thesis. The HPV-OPC study found an unexpectedly high prevalence of HPV 13 and 32 (Appendix D), which is associated with Heck's Disease. This Chapter reviews the literature on Heck's disease and provides an update on the trends, ethnic predispositions and treatment strategies.

This study is a recent update of the literature and is crucial to our study, based on the findings at baseline and 12-months of the HPV-OPC study. This is a systematic review which critically assesses the literature and illustrates the geographic distribution of Heck's Disease.

.2 PUBLICATION DETAILS

This paper has been published in the Journal of Public Health as: Sethi S, Ali A, Ju X, Antonsson A, Logan R, Jamieson L. An update on Heck's disease-a systematic review. J Public Health (Oxf). 2021 Jan 27:fdaa256. doi: 10.1093/pubmed/fdaa256. Epub ahead of print. PMID: 33501985.

.3 HIGHLIGHTS

- The review provides a comprehensive summary of the literature available on Heck's disease. There is an ethnic predisposition of this disease and a higher prevalence amongst the Indigenous populations of the world.
- The current systematic review found an increased incidence of Heck's disease in the European region.
- Pathways of transmission : HPV 13 or 32 is transmitted in a manner similar to that of other human papillomaviruses, by surface contact with the virus through a break in the mucosal barrier.

.4 STATEMENT OF AUTHORSHIP

Statement of Authorship

Title of Paper	An update on Heck's disease-a systematic review
Publication Status	☑ Published ☐ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and Unsubmitted w ork w ritten in manuscript style
Publication Details	Sethi S, Ali A, Ju X, Antonsson A, Logan R, Jamieson L. An update on Heck's disease-a systematic review. J Public Health (Oxf). 2021 Jan 27:fdaa256. doi: 10.1093/pubmed/fdaa256. Epub ahead of print. PMID: 33501985.

Principal Author

Name of Principal Author (Candidate)	Sneha Sethi		
Contribution to the Paper	Conceiving of Research question Data Analysis Manuscript writing Editing and Revisions Paper submission for publication Correspondence with Editors in the publication process		
Overall percentage (%)	75%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	20/07/2021

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Anna Ali		
Contribution to the Paper	Input in Methodology Data Analysis Interpreation and Writing of results Revision of Manuscript		
Signature		Date	20/07/2021

Name of Co-Author	Xiangqun Ju		
Contribution to the Paper	Orientation on formulation of Research question Revision of Methodology Input in theory application Input in Interpretation of results Revision of Manuscript		
Signature		Date	20/07/2021

Please cut and paste additional co-author panels here as required.

Name of Co-Author	Annika Antonsson
Contribution to the Paper	Revision of Methodology Input in theory application Input in Interpretation of Results Revison of Manuscript
Signature	Date 20/07/2021

Name of Co-Author	Richard Logan
Contribution to the Paper	Revision of Methodology Input in theory application Input in Interpretation of results Revision of Manuscript
Signature	Richard Logan Date 20/9/2021

Name of Co-Author	Lisa Jamieson
Contribution to the Paper	Orientation on formulation of Research question Revision of Methodology Input in theory application Input in Interpretation of Results Revison of Manuscript
Signature	Date 20/07/2021

.5 PUBLICATION

Journal of Public Health | pp. 1–17 | doi:10.1093/pubmed/fdaa256

An update on Heck's disease—a systematic review

Sneha Sethi[1], Anna Ali[2], Xiangqun Ju[1], Annika Antonsson[3], Richard Logan[4], Lisa Jamieson[1]

[1] Australian Research Centre for Population Oral Health, Adelaide Dental School, University of Adelaide, Adelaide, Australia
[2] Robinson Research Institute, University of Adelaide, Adelaide, Australia
[3] QIMR Berghofer Medical Research Institute, Brisbane, Australia
[4] Adelaide Dental School, University of Adelaide, Adelaide, Australia
Address correspondence to Sneha Sethi, E-mail: sneha.sethi@adelaide.edu.au

ABSTRACT

Background Previous research has suggested an ethnic association of Heck's disease with a prominent genetic and familial inheritance pattern, but no systematic review has been reported, which has collected all the evidence in one paper. The aim was estimation of the updated age estimates and gender predilection of this disease and also questioning its proposed link to ethnic and geographical factors.

Methods Heck's disease from 1966 until present are tabulated, including various descriptive characteristics. After removal of duplicates and adhering to all the inclusion criteria, we shortlisted 95 case reports. The quality assessment of all included studies has been done following STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guidelines.

Results We found an age range of 3–92 years (mean: 23.1 years) with a male to female ratio of 3:4. Geographical distribution revealed one of the main findings of this study, which was an increased incidence of Heck's disease in the European region.

Conclusions As already observed and established, there is a much greater prevalence of this disease in the indigenous populations of the world and more research should be encouraged to understand the correct transmission and pattern of spread of this disease.

Keywords HPV 13, indigenous health, multifocal epithelial hyperplasia, oral disease, viral

Introduction

Heck's disease, also known as multifocal epithelial hyperplasia (MEH) or focal epithelial hyperplasia (FEH), is a rare benign oral condition. Mostly seen in females,[1] it clinically presents as soft, distinct, mostly multiple, smooth papules or nodules having the same colour as the surrounding mucosal epithelium,[2] and predominantly affecting the lower and upper labial mucosa and tongue, but frequently seen in other oral mucosal sites as well. Two clinical types have been described in the literature[1]: the papulonodular and the papillomatous type, also a characteristic 'cobblestone' appearance has been used to describe its clinical appearance.[1]

It is predominately caused by human papillomavirus (HPV) 13 or 32,[3,4] with some cases also reporting involvement of other HPV sub-types as well. Although usually a self-limiting and resolving condition, if the condition persists, it can significantly affect the quality of an individual's life, for example, chewing and eating abilities are compromised along with aesthetic concerns.[5] It primarily manifests in children,[5] which has been attributed to children's immature immune system and compromised ability to fight viral infections.[1] Adults with Heck's disease typically have fewer and flatter papules compared with children.[6] Most reported cases of Heck's disease have been among females.[1]

Initially cases were only observed among Native Americans, Inuit and some African populations.[2,7] More contemporary cases have been reported around the world. An association between ethnicity and Heck's disease has been suggested,[8,9] as well as genetic links. For example, >80%

Sneha Sethi, PhD student
Anna Ali, PhD student
Xiangqun Ju, Research Officer
Annika Antonsson, Associate Professor
Richard Logan, Professor and Dean, Adelaide Dental School
Lisa Jamieson, Professor and Director of Indigenous Oral Health Unit

Table 1 Chronological journey of Heck's disease

1881	*The first known communication on MEH was recorded*
1894	Multifocal papillomatous lesions of the oral mucosa was first described in Eskimos
1956	First reported in Latin American literature in 1956
1961	Identified a patient with this condition in New Mexico
1962	Description of lesion in his article 'warts of the oral cavity' in a condition seen in Guatemala. Named it verrucae of the oral cavity
1964	Description of the clinical varieties of the disease changing from a single papule to widespread verrucoid lesions and also the presence of binucleated cells and cytolysis in histopathologic examinations supporting the hypothesis of viral origin
1965	Described a focal epithelial hyperplasia of the labial, buccal and lingual mucosa in American Indians. Described 15 cases in Navajo Indian children and four cases in other American Indian ancestry. Coined the term 'Hecks disease'
1966	Suggestion of a genetic linkage of the disease and inheritance as a recessive trait
1969	First cases to be described from Bolivia
1969	Mention of familial predisposition as an aetiological factor
1971	First to revealing viral particles (HPV) in MEH lesions via electron microscopy
1971	First case series (seven cases) reported from Iraq, suggesting people apart from American Indians are also affected
1972	HPV lesions first reported in chimpanzee
1972	Detailed light and electron microscopic study of Heck's lesions.
1975	First ultrastructural study of MEH lesions, showing inclusion bodies of lamellar pattern called 'Myelin Bodies'/'Myelin Figures' and suggested an aetiology other than viral and lysosomal involvement was hypothesized
1975	First case of focal epithelial hyperplasia reported in Amsterdam
1976	First reported case in France
1977	37 cases reported in South Africa, with a detailed study of its clinical, microscopic and ultrastructural features
1978	First case series with follow up reported from Israel with Libyan origin, strongly suggesting a genetic connection and ethnic predilection
1979	Ultrastructural study on focal epithelial hyperplastic lesions of the oral cavity in rabbits
1980	Isolation of virus-like particles with morphology of papilloma virus group from lesions
1981	Suggestion of viral aetiology to Heck's disease
1981	First case of Greece reported in a 56-year-old white female
1982	'bronze-age ax rete ridge patterns' observed in FEH lesions
1983	Human papillomavirus (HPV) type 13 was first cloned from DNA isolated from an oral focal epithelial hyperplasia (FEH) lesion from Turkish patient
1983	First cases of Africa and Nigeria presented (first of Black Africans)
1984	HPV DNA testing showed reaction with both HPV 13 and 18, suggesting a new variant responsible for MEH
1984	First case series from Sweden reported (nine cases)
1986	First case of FEH in Iran reported
1987	Association with HPV 32
1987	Demonstrated that HPV 13 DNA was present as unintegrated circular DNA
1991	Description of identical types of HPV in affected siblings and first-degree relatives of affected patients, supporting both viral aetiology and genetic predisposition
1991	Case reported with HPV 13 associated with perianal cancer and Bowenoid papulosis
1991	Performed research involving designing of primers for HPV 13 sequencing and detection by polymerase chain reaction. Conditions for PCR were standardized for this set of primers
1993	First three cases of Nairobi, Kenya reported
1993	HPV and mucosal carcinogenesis has been suggested, but evidence is unavailable and fact remains unclear
1993	Performed study with conclusion of genetic familial basis of disease
1994	The name multifocal papilloma virus epithelial hyperplasia was suggested
2002	Investigated E6 and E7 behaviour in cells of MEH tissues and concluded the benign nature of HPV 32 lesions
2003	1465 cases of this disease found in 5–20-year-old students from the Morrope–Lambayeque region in Peru (largest series reported)
2004	Assessed association of HLA-DR4 allele with HPV infection
2004	Described the first report of FEH successfully treated with topical imiquimod

(Continued)

Table 1 Continue

1881	*The first known communication on MEH was recorded*
2005	First repot of multiple conjunctival papilloma's similar to Heck's by HPV 13
2005	A shorter and more appropriate name, 'multifocal epithelial hyperplasia' (MEH), was introduced
2006	The first case–control study conducted in the world that demonstrates the association between HPV 13 and FEH (Embera–Chami community)
2009	Seven cases of Heck's reported in Khorasan district of Iran, suggesting Asian spread of disease as well
2012	Proposal of the vaccine cross-protection mechanism between HPV strains with genomic similarity
2013	First report of a case with two independent HPV infections (HPV 32 and HPV 16) co-existing at different sites in the same person
2015	First case of Heck's reported with HPV 40
2019	Published findings of Heck's disease in a bonobo, 30 years after infection. They indicated different behaviour in different animals with different pattern of remission and recurrence signifying the significance of evolution
2019	An immunohistochemical study showed both included cases of Heck's disease to show positivity for HPV 13, cytokeratin 4 and cytokeratin 13

of one population with Heck's disease had a positive human leukocyte antigen-DR locus.[10–13]

Cases of MEH have been reported with the presence of other diseases, including lepromatous leprosy,[14] rheumatoid arthiritis,[15] leucocyte adhesion deficiency[16] and immunosuppressive diseases (human immunodeficiency viral infection (HIV) and non-HIV).[17–27] Non-human primates have also shown signs of Heck's disease, with some research investigating the origin and evolution of this viral disease.[28–31] A table depicting the chronology of this disease with its important scientific landmarks is shown in Table 1,[10,32–77] which spans from 1881 to 2019.

Commonly suggested differential diagnosis of Heck's disease includes condyloma acuminatum,[78–80] verruca vulgaris, squamous papilloma, oral florid papillomatosis, diffuse epithelial hyperplasia and Cowden syndrome.[78,79] More uncommon differential diagnoses include white sponge nevus,[81] multiple endocrine neoplasia syndrome type III, neurofibromatosis, tuberous sclerosis, epidermal nevus syndrome,[80] Fordyce's granules and morsicatio buccarum (chronic cheek biting).[82]

Prevalence

This review includes a comprehensive tabular representation of data collected from all the studies, which includes individual case reports,[11,33,36–116] but we also came across a few studies, which have previously estimated the prevalence estimates of MEH. The literature on Heck's disease includes mainly individual case reports. The prevalence among some populations has been reported in some geographic regions.

The maximum number of reported cases has been in South America, a region with great ethnic diversity. One of the earliest studies dates back to 1980, where the prevalence of Heck's disease was reported to be 7.4% in the Xavante and Bororo Indian tribes[83] in Brazil. Then, in 1994, more than a hundred cases of Heck's disease were identified in Guatemala City and its neighbouring rural areas, predominantly affecting the younger population (age 20 years or younger).[33] A report in the Amazon reported a 21% prevalence among Waimiri Atroari Indians,[6] 1.6% prevalence in Mexican mestizo populations[85] and 32.3% prevalence in Nahuatl children.[86] In 1998, the prevalence of Heck's disease in Embera Chami from Jardin, Antioquia, Colombia was 7.5%,[87] which increased to 13% in 2006.[71] A study investigating the Mayan area in South Mexico reported a prevalence of 0.1%, with cases among children aged mostly 7 years and younger.[11]

Other studies have been reported from Europe, South Africa and Canada. In South Africa, the annual prevalence of Heck's disease in the Khoi-San indigenous population[88] was reported as 7–13%, whereas in southwest Greenland,[89] 19.4% of the 460 Indigenous Nanortalik population showed clinical manifestations of FEH. In Canada, two studies were performed almost a decade apart (1972 and 1981). The prevalence of Heck's disease ranged from 8.6 to 18.6%, respectively.[7,90] In Sweden, a prevalence of 0.11% was reported in the general Caucasian population, with most cases being aged 45 years or more.[9] In Germany, Henke *et al*.[91] described 17 cases of Heck's disease, with the age of patients being 28–76 years. In Argentina, 2174 participants were examined, with a prevalence of Heck's disease of 0.02% for the whole sample and 0.09% for the province of Jujuy reported.[92]

Factors associated with Heck's disease

Along with a confirmed HPV aetiology, a genetic and ethnic links have been established with Heck's disease, and also many social and environmental factors and behaviours are also

Table 2 Quality of reporting of studies included in the review (according to STROBE guidelines)

S. No.	Author	Year of publication	Quality of study
1	Hettwer and Rodgers	1966	Medium
2	Phillips[118]	1968	Medium
3	Waldman and Shelton	1968	Medium
4	Fischman[119]	1969	High
5	Schock[120]	1969	Medium
6	Tan[121]	1969	High
7	Bradnum[122]	1970	Medium
8	Adkins *et al.*[123]	1971	Medium
9	Hanks *et al.*	1972	High
10	Greenspan[124]	1974	Medium
11	Van der Waal *et al.*	1975	Medium
12	Lindeberg[125]	1976	Medium
13	Starink[126]	1977	Medium
14	Edwards[127]	1978	High
15	Goodfellow[128]	1979	Medium
16	Stiefler *et al.*	1979	High
17	Kohn and Kohn	1980	High
18	Acevedo *et al.*[129]	1981	High
19	Syrjänen[130]	1984	Medium
20	Hallmon[131]	1985	Medium
21	Betancourt Castro[132]	1988	Medium
22	Felipe Jaramillo[133]	1991	High
23	Bon[134]	1992	Medium
24	Khan *et al.*	1992	High
25	Khan *et al.*	1992	Medium
26	Chindiya[135]	1993	Medium
27	Chindiya	1993	High
28	Chindiya	1993	Medium
29	Cohen[136]	1993	High
30	Obalek *et al.*	1993	High
31	Obalek *et al.*	1993	High
32	Landells[137]	1994	High
33	Marvan and Firth	1998	Medium
34	Flaitz[138]	2000	Medium
35	Halsley-Royster[139]	2001	Medium
36	Kose[140]	2001	Medium
37	Steinhoff *et al.*	2001	Low
38	Gulli[141]	2002	Medium
39	Akyol *et al.*	2003	High
40	Jayasooriya *et al.*	2004	Medium
41	Jayasooriya *et al.*	2004	Medium
42	Durso[142]	2005	Medium
43	Segura Saint-Gerons *et al.*	2005	Medium
44	Borborema-Santos *et al.*[146]	2006	Medium
45	Martins[143]	2006	Medium
46	Binder[144]	2007	Medium
47	Namazi[145]	2007	Low

(Continued)

Table 2 Continue

S. No.	Author	Year of publication	Quality of study
48	Santos	2007	Medium
49	Yasar *et al.*	2009	Medium
50	Bennet and Hinshaw	2009	High
51	Bombeccari[147]	2009	Medium
52	Lourdes dos Santos-Pinto[148]	2009	Medium
53	Kutcher *et al.*	2009	Medium
54	Ricardo[149]	2010	Medium
55	Artac *et al.*	2010	Medium
56	De La Hera[150]	2010	High
57	Feller *et al.*	2010	Medium
58	Hall *et al.*	2010	Medium
59	Hashemipour[151]	2010	Medium
60	Saunders *et al.*	2010	Medium
61	Saunders *et al.*	2010	Medium
62	Gultekin[152]	2011	High
63	Gultekin	2011	High
64	Gultekin	2011	High
65	Hansen[153]	2011	Medium
66	Martinez-Escala[154]	2011	High
67	Ozden[155]	2011	Medium
68	Puriene[156]	2011	Low
69	Al-Sheddi[157]	2012	Medium
70	Liu[158]	2012	High
71	Liu	2012	High
72	Ricardo[159]	2012	Medium
73	Prabhat[160]	2013	Medium
74	Meissner *et al.*	2014	Medium
75	De Castro[161]	2014	Medium
76	Eshgi[162]	2014	High
77	Galanakis[163]	2014	Medium
78	Park[164]	2014	Medium
79	Patterson *et al.*	2014	Medium
80	Ruiz[165]	2014	High
81	Akoglu[166]	2015	Medium
82	Asha[167]	2015	Medium
83	Gernigniani[168]	2015	Medium
84	Ghalayani[169]	2015	High
85	Kubiak[170]	2015	Medium
86	Mansouri[171]	2015	Medium
87	Brehm[172]	2016	Medium
88	De Castro[173]	2016	Medium
89	Shamloo[174]	2016	Low
90	Agnew *et al.*	2017	High
91	Caldeira[175]	2018	Low
92	Loureiro[176]	2018	Low
93	Do Vale[177]	2019	Medium
94	Kreuter[178]	2018	High
95	Nallanchakrava *et al.*	2018	High

Table 3 Description of the data extracted (patient characteristics) from articles included in the study

S. No.	*Age*	*Gender*	*Duration*	*Family involvement*	*Site of lesion*	*Author*	*Year of publication*	*Country*	*Ethnicity*
1	9	F	NS	NS	Lower lip and buccal mucosa	Hettwer and Rodgers	1966	Hawaii, USA	Polynesian
2	10	F	12 months	NS	Buccal mucosa and lips	Phillips	1968	South America	Peurto Rican
3	56	F	NS	NS	Lower lip	Waldman and Shelton	1968	New York, USA	Caucasian
4	30	M	4 years	None	Buccal, labial and lingual mucosa	Fischman	1969	Paraguay, South America	Indigenous Indian
5	11	F	NS	Mother	Lower lip, commissures and cheeks	Schodr	1969	USA	Indian
6	12	M	15 months	None	Tongue, labial and buccal mucosa	Tan	1969	Chicago, USA	Mexican Indian
7	36	M	7 years	NS	Alveolar ridges, cheeks, tongue and lower lip	Bradnum	1970	Newcastle, England	Scottish
8	22	F	18 months	NS	Lower lip, buccal mucosa and alveolar mucosa	Adkins *et al.*	1971	Australia	Aboriginal
9	25	M	20 years	Child	Lower lip mucosa and tongue	Hanks *et al.*	1972	Cochabamba, Bolivia	Mestizo Indian
10	65	F	50 years	NS	Lower lip mucosa and tongue	Greenspan	1974	UK	Caucasian
11	12	M	NS	Sister	Lower and upper lip, buccal mucosa, gingiva and tongue	Van der Waal *et al.*	1975	Amsterdam, Europe	Surinamese
12	36	F	NS	NS	Buccal gingiva and lower lip	Lindeberg	1976	Norway	Norwegian
13	9	F	NS	Brother	Upper and lower lips	Starink	1977	Netherlands	Surinamese
14	11	F	5 years	Brothers	Lower labial mucosa and tongue	Edwards	1978	Abu Dhabi, Middle East	Abu Dhabi
15	26	M	NS	None	Lower lip, upper lip and tongue	Goodfellow	1979	UK	West Indian
16	31	M	6 years	Mother	Lower lip	Stiefler *et al.*	1979	Brooklyn, USA	Puerto Rican
17	69	F	1 year	None	Left buccal mucosa	Kohn and Kohn	1980	New York, USA	Caucasian
18	12	M	5 years	None	Buccal mucosa, lips and tongue	Acevedo *et al.*	1981	Nicaragua, Central America	Indian
19	30	F	NS	NS	Left commissure	Syrjänen	1984	Finland	Finnish
20	12	F	18 months	NS	Entire mucosa	Hallmon	1985	Texas, USA	Navajo and Comanche Indian
21	57	M	NS	None	Upper lip and tongue	Betancourt Castro	1988	Brazil, South America	Indigenous descent
22	12	F	1 year	Mother	Labial mucosa	Felipe Jaramillo	1991	South America	Puerto Inirida
23	14	F	6 years	Brother	Upper and lower lip	Bon	1992	NS	Italian
24	10	M	5 years	None	Lower lip	Khan *et al.*	1992	Peshawar, Pakistan	Afghan
25	10	F	2 years	NS	Lower lip and upper labial mucosa	Khan *et al.*	1992	Peshawar, Pakistan	Chitral
26	11	F	8 months	NS	Lips, buccal mucosa and tongue	Chindiya	1993	Nairobi, Kenya	African
27	8	F	10 months	Grandmother	Lips, buccal mucosa and tongue	Chindiya	1993	Nairobi, Kenya	African
28	12	F	7 years	NS	Lower lip	Chindiya	1993	Nairobi, Kenya	African
29	8	F	1 year	Sister	Lower lip and tip of tongue	Cohen	1993	Houston, USA	Mexican
30	7	F	1 year	None	Tongue	Obalek *et al.*	1993	Warsaw, Poland	Polish
31	9	F	7 years	None	Lip buccal mucosa and tongue	Obalek *et al.*	1993	Warsaw, Poland	Polish

(Continued)

Table 3 Continue

S. No.	Age	Gender	Duration	Family involvement	Site of lesion	Author	Year of publication	Country	Ethnicity
32	12	M	9 months	Unde	Upper and lower labial mucosa	Landells	1994	Canada	Somalia, Black
33	39	M	NS	NS	Lower lip and buccal mucosa	Marvan and Firth	1998	Melbourne, Australia	Caucasian
34	5	F	NS	None	Widespread mucosal	Flaitz	2000	USA	Hispanic
35	19	F	NS	Father	Lower labial mucosa and tongue	Haisley-Royster	2001	North Carolina, USA	Haliwa-Saponi tribe
36	21	M	2 years	NS	Tongue and lips	Kose	2001	Turkey	Caucasian
37	4	M	1 year	NS	Lips and oral mucosa	Steinhoff *et al.*	2001	Not specified	Not specified
38	12	F	8 months	NS	Upper and lower labial mucosa	Guill	2002	Texas, USA	Native American
39	17	M	7 years	Brother	Lower lip buccal mucosa, gingivae and the tongue	Akyol *et al.*	2003	Ankara, Turkey	Turkish
40	42	F	25 years	None	Upper and lower lingual and buccal mucosa	Jayasooriya *et al.*	2004	Sri Lanka	NS
41	65	M	NS	None	Buccal mucosa	Jayasooriya *et al.*	2004	Sri Lanka	NS
42	21	F	10 years	NS	Cheek, mucosa, lip mucosa and tongue	Durso	2005	South America	South American Indian
43	9	F	NS	NS	Retro commissural area and mucosa of the lower lip	Segura Saint-Gerons *et al.*	2005	Spain	Saharan
44	17	M	NS	Siblings	Lower lips and upper lips	Borborema-Santos *et al.*	2006	Brazil, South America	Central Amazonian Indian
45	14	F	NS	None	Gingival lesion	Martins	2006	Brazil, South America	Brazilian Xavante Indian
46	3	M	NS	NS	Upper and lower lips	Binder	2007	Germany	Black African
47	7	F	NS	None	Oral mucosa	Namazi	2007	Not specified	NS
48	18	F	2 years	NS	Buccal mucosa	Santos	2007	Rio, South America	Potiguar Indian
49	5	F	1 year	None	Hard palate, buccal mucosa, upper and lower lips	Yasar *et al.*	2009	NS	NS
50	9	F	1 year	None	Left buccal, gingival and labial mucosa	Bennet and Hinshaw	2009	Wisconsin, USA	Hispanic
51	13	M	NS	Mother	Lower lip and cheek mucosa	Bombeccari	2009	Milan, Italy	Bolivian
52	3	M	NS	None	Maxillary anterior	Lourdes dos Santos-Pinto	2009	South America	Not specified
53	28	F	NS	NS	Right buccal mucosa	Kutcher *et al.*	2009	USA	African-American
54	10	F	1 year	None	Buccal mucosa and tongue	Ricardo	2010	South America	NS
55	12	F	NS	None	Left buccal mucosa	Artac *et al.*	2010	Konya, Turkey	Turkish

(Continued)

Table 3 Continue

S. No.	Age	Gender	Duration	Family involvement	Site of lesion	Author	Year of publication	Country	Ethnicity
56	21	M	11 years	None	Upper and lower lips	De La Hera	2010	Latin America	Paraguayan
57	11	F	5 years	Mother	Upper and lower lips	Feller *et al.*	2010	South Africa	Not specified
58	13	M	NS	Sisters	Tongue and lips	Hall *et al.*	2010	Australia	Somalia
59	12	F	8 years	NS	Tongue and buccal mucosa	Hashemipour	2010	Iran	Persian
60	8	F	NS	Siblings	Upper and lower buccal mucosa as well as on the left lateral tongue	Saunders *et al.*	2010	Guyana	Wapishana Tribe
61	11	M	NS	None	Tongue and bilateral lesions on the upper buccal mucosa	Saunders *et al.*	2010	Guyana	Wapishana Tribe
62	8	F	14 months	Father	Upper and lower lip and tongue	Gultekin	2011	Turkey	Caucasian
63	16	M	9 months	None	Upper lip	Gultekin	2011	Turkey	Caucasian
64	17	F	6 months	None	Upper and lower lip	Gultekin	2011	Turkey	Caucasian
65	57	F	50 years	NS	Tongue and oral mucosa	Hansen	2011	Oslo, Norway	Norwegian
66	12	M	8 months	None	Upper and lower labial mucosa	Martinez-Escala	2011	Barcelona, Spain	Ecuador
67	7	F	6 months	NS	Upper labial and left buccal mucosa	Ozden	2011	Samsun, Turkey	Caucasian
68	15	F	NS	NS	Cheek and lip mucosa	Puriene	2011	Žalgiris, Lithuania	NS
69	43	F	NS	NS	Upper and lower labial mucosa and right and left buccal mucosa	Al-Sheddi	2012	Saudi Arabia	Arabic
70	7	F	1 year	None	Lips and buccal mucosa	Liu	2012	China	Chinese
71	33	F	1 month	None	Labial mucosa and gingiva	Liu	2012	China	Chinese
72	7	F	8 months	None	Labial mucosa and buccal mucosa	Ricardo	2012	Colombia, South America	Not specified
73	65	F	2 months	7 months	Labial gingiva and palate	Prabhat	2013	India	Not specified
74	55	M	1 year	NS	Tongue and labial mucosa	Meissner *et al.*	2014	Germany	Not specified
75	6	M	6 months	NS	Upper and lower lips	De Castro	2014	Brazil, South America	Brazilian indigenous
76	47	F	37 years	None	Buccal mucosa, lower lip and tongue	Eshgi	2014	Iran	Iranian
77	37	M	2 years	NS	Upper and lower labial mucosa	Galanakis	2014	Rome, Europe	African
78	53	M	1 month	NS	Buccal-attached gingiva	Park	2014	Seoul, Republic of Korea	Korean
79	52	M	NS	NS	Buccal and labial mucosa and lateral tongue	Patterson *et al.*	2014	USA	Caucasian
80	14	M	13 years	Brother	Cheek mucosa, lip mucosa and tongue	Ruiz	2014	Mexico, South America	North American Indian
81	17	M	NS	Mother	Buccal mucosa and lips	Akoglu	2015	Anatolia, Turkey	Turkish

(Continued)

Table 3 Continue

S. No.	Age	Gender	Duration	Family involvement	Site of lesion	Author	Year of publication	Country	Ethnicity
82	8	M	1 year	NS	Tongue	Asha	2015	Chennai, India	NS
83	11	F	1 year	NS	Upper and lower lips and bilateral cheek mucosa	Gemigniani	2015	Barcelona, Spain	Haitian
84	30	M	6 months	Niece	Buccal mucosa, lower lip and tongue	Ghalayani	2015	Turkey	Afghan
85	56	M	NS	None	Tongue and lower lip	Kubiak	2015	Wroclaw, Germany	Caucasian
86	35	M	NS	None	upper and lower labial mucosa and buccal mucosa	Mansouri	2015	Iran	Iranian
87	11	F	NS	None	Lower lip, tongue and buccal mucosa	Brehm	2016	USA	Hispanic
88	57	M	NS	None	Lip and tongue	De Castro	2016	Brazil, South America	Indigenous Brazilian
89	92	M	2 months	NS	Retro commissure of his lower lip	Shamloo	2016	Not specified	Not specified
90	5	F	3 weeks	Brother	Labial mucosa, commissures, tongue and attached gingiva	Agnew *et al.*	2017	Australia	Sudanese
91	42	F	NS	NS	Bilateral buccal mucosa	Caldeira	2018	—	Amazonian descent
92	47	F	1 month	NS	Tongue and bilateral buccal mucosa	Loureiro	2018	Not available	Not available
93	52	M	NS	NS	Entire oral mucosa	Do Vale	2019	South America	Asian descent
94	7	M	2 years	None	Lower labial mucosa	Kreuter	2018	Germany	Angola
95	5	M	3 years	None	Lower labial mucosa	Nallanchakrava *et al.*	2018	Telengana, India	Indian

NS, not specified; M, male; F, female.

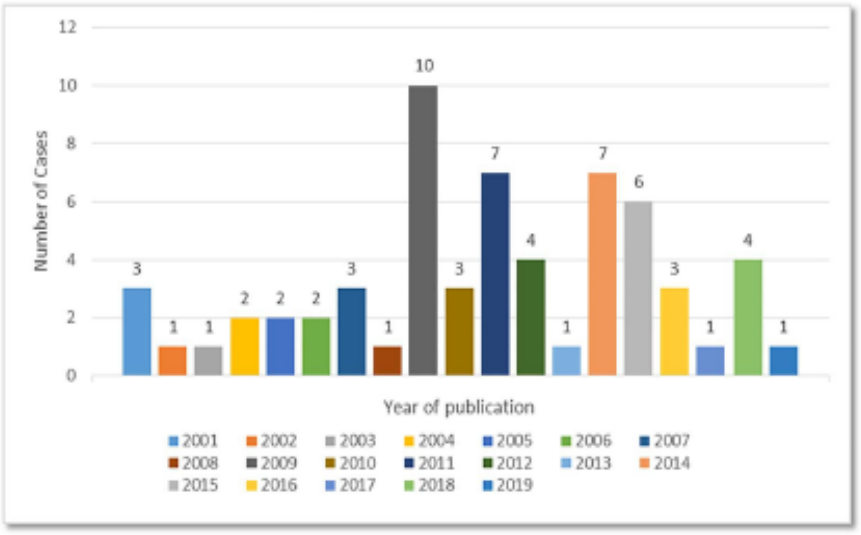


Fig. 1 Number of reported cases of Heck's disease per year in last 20 years (2001–19).

significantly associated. The prevalence differs substantially according to geographical location,[93] whether a city is rural or urban and its population size. A higher prevalence of Heck's disease has been reported among the socially disadvantaged. These include populations with low annual incomes,[33,85,94] malnutrition[33,39,94] and overcrowded living conditions.[33,94] Certain household behaviours have been linked with familial incidence of Heck's disease, including sharing of food,[4] utensils[85] and toothbrushes.[95] It has been observed that HPV 13 can be transmitted via saliva, and hence the use of contaminated oral hygiene aids and kitchen cutlery can lead to spread of the disease from one member of the family to another.[96]

Poor oral hygiene and inconsistent hygiene habits have been associated with Heck's disease.[4,33,85] Medical conditions that lead to suppressed immune status are also associated with Heck's disease, including adenosine deaminase deficiency, which causes severe combined immunodeficiency in infants.[97] Patients on anti-retroviral therapy are frequently seen with symptoms of FEH.[98]

Diagnostic trends

Biopsy is considered the gold standard for diagnosis of any pathology, including Heck's disease. Various histological features, including koilocytes and inclusion bodies are pathognomonic of HPV-related diseases, also mitosoid cells (cells with fragmented nucleus resembling a mitotic figure) are prominently, but not abundantly, seen in the epithelium of the tissue sections.[60,85,99]

Immunohistochemical methods are popular for detecting HPV 13 and 32. Although the method is highly sensitive (80%),[101] the specificity is less (70%)[91] due to the lack of specific antibodies. Currently, the standard HPV screening kits do not contain probes for specifically testing HPV 13 and 32, which suggest there may be many unreported and undiagnosed cases using this technique. Another method of detection is *in situ* hybridization, and so far this method has the least drawbacks and overcomes the shortcomings of the immunohistochemical methods.[91]

Treatment modalities

Because Heck's disease appears to manifest more frequently in children, many cases of children with different treatment options have been reviewed. For paediatric patients, the general consensus is to 'wait and watch', as the condition will most probably resolve on its own, and it is not necessary to expose young children to harsh treatments and medications.[102]

Conservative treatment options for adults include vitamin supplements,[55,103] oral tretinoin application,[104] topical keratinolytic agents[105] and interferon-β.[106] Topical imiquimod (immune response modifier) have also been used with favourable results[5,68] (and unfavourable results[108]). Interferon-α has been used as a topical agent, intralesional and systemic medicament,[5,80] with varying degrees of success.[107] Trichloroacetic acid is one of the most useful non-invasive approaches to resolving the Heck's disease lesions.[110] Many methods of application have been suggested, ranging from 50 s application followed by a wash with bicarbonate

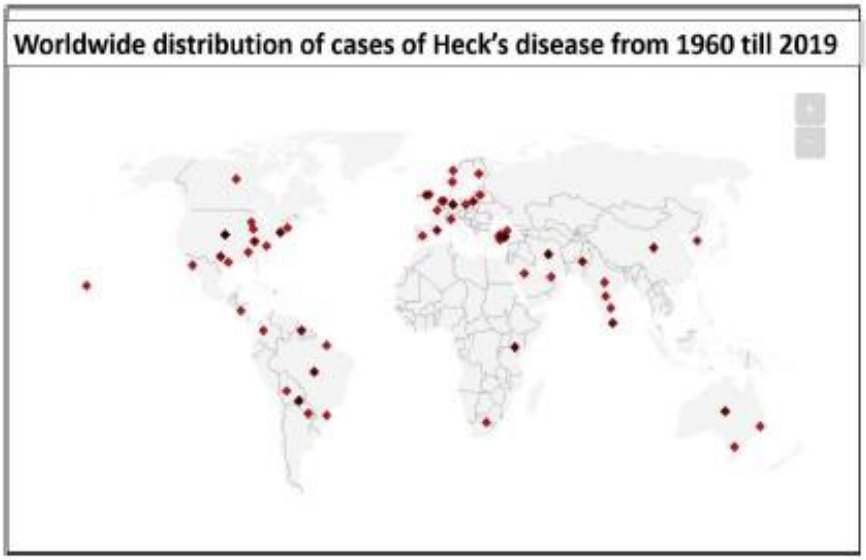


Fig. 2 Worldwide geographical distribution of reported cases of Heck's disease from 1960 to 2019.

solution[109] to three applications within 45 days for 30 s each.[110]

Surgical excision using different energy sources is the treatment option for non-resolving, aesthetically unpleasing lesions. Along with classic surgical excision,[5,111] CO_2 laser ablation methods[107,108,112] and electro cauterization[113] have been used with success. Cryotherapy has shown mixed results.[5,114,115] Radiotherapy is a less popular method of treatment, because it causes anaplastic change in the cells, and therefore risks a malignant transformation or secondary occurrence.[116,117]

Cases reports in literature

A structured literature search was performed using the search engines PubMed, SCOPUS, Web of Science, Embase, OVID and Science Direct from 1966 to 15 January 2020. The search strategy included a combination of subject terms and free text terms, and these terms were combined with 'OR' and 'AND' operators. The various term used included HPV [Text Word] OR 'papillomaviridae' [MeSH Terms] OR 'human papillomavirus' [MeSH] OR 'human papillomavirus' [Text Word] OR 'human papillomavirus 13' [MeSH Terms] OR human papillomavirus 13 [Text Word] OR 'human papillomavirus 32' [MeSH Terms] OR human papillomavirus 32 [Text Word] OR papillomavirus [Text Word] OR 'Heck's Disease' [Text Word] OR 'Heck's disease' [MeSH Terms] OR 'Focal Epithelial Hyperplasia' [Text Word] OR 'Focal Epithelial Hyperplasia' [MeSH Term] OR 'Multifocal Epithelial Hyperplasia' [Text Word] OR 'MEH' [Text Word]. All identified references were imported into Endnote X4 software and managed there. The bibliographies of identified research and review articles were checked for additional relevant studies. Initial searches based on specific terms for Heck's disease failed to retrieve some known studies; therefore, broader terms for MEH and FEH were used.

Inclusion criteria for articles to be included were as follows (Supplementary Material A1—PRISMA flowchart): English language, full-text available, specific to Heck's disease (HPV 13, 32) and case reports with basic demographics of the patients described. We also removed the case series reported as we were focussing on the isolated case reports, which have been reported in literature. Duplicates were removed, as were articles that, on further assessment, did not adhere to the inclusion criteria.

Initial searches yielded 1200 articles, out of which 629 were duplicates and were removed. The total number of articles, which were relevant to our research was 165, and 116 case reports/published studies were included and analysed to extract information on age, sex, ethnicity, site and familial tendency. After extracting data and further analysing the articles, 21 articles were further discarded due to insufficient data in one or more fields. The literature searches were performed by two investigators independently (SS and A. Ali); any discrepancies were cleared by mutual discussions and consent and in case of a conflict, a third investigator's (LJ) opinion was taken.

Quality of study reporting

To assess the quality of reporting of the published studies, we adapted the STROBE (STrengthening the Reporting of

OBservational studies in Epidemiology) guidelines[117] by selecting recommendations most relevant to rare diseases (Supplementary Material A2). The quality of reporting was summarized in Table 2. The following information was extracted from studies: age, gender, duration of lesions, site of lesions, ethnicity of patient, and country of reporting case, author and the year of publication.

The patient characteristics and descriptions were tabulated and analysed (Table 3), we included cases of FEH starting from 1966[39] to 2018[116]; the age of the cases ranged from 3 to 92 years, with a mean age of incidence as 23.1 years (95% CI: 19.10–26.98). There were 54 cases of females and 41 males, giving a male to female ratio of 3:4. According to the data collected, 25.3% (24 cases) reported some familial involvement or history of any other family member having similar lesions in the oral cavity. A total of 37 cases (38.9%) did not have this information available, and 34 cases (35.8%) clearly stated no familial involvement.

A total of 34 out of 95 cases did not report the duration of their lesions. For the remaining 65 reports, the duration of lesions ranged from 0.06 (3 weeks) to 50 years, with a mean of 5.37 years (95% CI: 2.7–8.04). We categorized the cases into three groups according to year of publication: 1960–80, 1981–2000 and 2011 until present. A total of 17 cases were reported in 1960–80, 17 in 1981–2000 and 61 cases in 2011–present (Fig. 1).

For visualization of the global prevalence of the disease, we plotted a scatter dot map from the geographical information gathered from these 95 cases (Fig. 2). The darker shade of the dot shows the increased number of cases from that particular region. We saw a large proportion of the reported cases belonged to the European region, with quite a few in the American continents as well. This can also be explained by the number of published reports from these regions.

Conclusion

Heck's disease is a rare disease and more awareness about this disease is encouraged in health practitioners, especially dentists. The lesions are asymptomatic and usually resolve spontaneously; hence, the reported incidence is quite low and there is a possibility of a much higher number of cases who are carrying the type (13 or 32) of HPV and are not recorded. As already observed and established, there is a much greater prevalence of this disease in the indigenous populations of the world and more research should be encouraged to understand the correct transmission and pattern of spread of this disease.

Supplementary Data

Supplementary data are available at the *Journal of Public Health* online.

Acknowledgement

Not applicable.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and material

Not applicable.

Conflict of interest

None declared.

Funding

Not applicable.

Authors' contributions

SS collected data and performed selection of articles to be included for critical analysis. A. Ali also proof read the articles to avoid bias. SS, XJ, A. Ali and LJ were involved in analysis and interpretation of results. AA, XJ, RL and LJ proof read manuscript and were actively involved in drafting the paper. All authors read and approved the final manuscript.

Disclosures

None.

Abbreviations

HPV, human papillomavirus; MEH, multifocal epithelial hyperplasia; FEH, focal epithelial hyperplasia; HIV, human immunodeficiency virus.

References

1 Agnew C, Alexander S, Prabhu N. Multifocal epithelial hyperplasia. *J Dent Child* 2017;**84**(1):47–9.

2 Witkop CJ Jr, Niswander JD. Focal epithelial hyperplasia in Central and South American Indians and Ladinos. *Oral Surg Oral Med Oral Pathol* 1965;**20**(2):213–7.

3 Kumaraswamy K, Vidhya M. Human papilloma virus and oral infections: an update. *J Cancer Res Ther* 2011;**7**(2):120–7.

4 Borborema-Santos CM, Castro MM, Santos PJ *et al.* Oral focal epithelial hyperplasia: report of five cases. *Braz Dent J* 2006;**17**(1):79–82.

5 Yasar S, Mansur AT, Serdar ZA *et al.* Treatment of focal epithelial hyperplasia with topical imiquimod: report of three cases. *Pediatr Dermatol* 2009;**26**(4):465–8.

6 Benevides Dos Santos PJ, Navarro Bessa CF, Ferreira De Aguiar MC, Vieira Do Carmo MA. Cross-sectional study of oral mucosal conditions among a central Amazonian Indian community, Brazil. *J Oral Pathol Med* 2004;**33**(1):7–12.

7 Jarvis A, Gorlin RJ. Focal epithelial hyperplasia in an Eskimo population. *Oral Surg Oral Med Oral Pathol* 1972;**33**(2):227–8.

8 Praetorius-Clausen F. Rare oral viral disorders molluscum contagiosum, localized keratoacanthoma, verrucae, condyloma acuminatum and focal epithelial hyperplasia. *Oral Surg* 1972;**34**:604–18.

9 Axéll T, Hammarström L, Larsson A. Focal epithelial hyperplasia in Sweden. *Acta Odontol Scand* 1981;**39**(4):201–8.

10 Garcia-Corona C, Vega-Memije E, Mosqueda-Taylor A *et al.* Association of HLA-DR4 (DRB1*0404) with human papillomavirus infection in patients with focal epithelial hyperplasia. *Arch Dermatol* 2004;**140**(10):1227–31.

11 García IAC, Espinosa JC, Del Rosario González Losa M. Multifocal epithelial hyperplasia. A report of 71 cases. *Dermatol Cosmet Med Quir* 2011;**9**(3):176–80.

12 Spelten B, Großendorf-Conen E-I, Rübben A. Human leukocyte antigen class II alleles and natural history of HPV 2/27/57-induced common warts. *Arch Dermatol Res* 2004;**296**(3):105–11.

13 Akoğlu G, Metin A, Ceylan GG *et al.* Focal epithelial hyperplasia associated with human papillomavirus 13 and common human leukocyte antigen alleles in a Turkish family. *Int J Dermatol* 2015;**54**(2):174–8.

14 Jacyk W, Lechner W. Focal epithelial hyperplasia in a patient with lepromatous leprosy. *Z Hautkr* 1983;**58**(20):1481–92.

15 Waldman GH, Shelton DW. Focal epithelial hyperplasia (Heck's disease) in an adult Caucasian. *Oral Surg Oral Med Oral Pathol* 1968;**26**(1):124–7.

16 Mealey BL, Hallmon WW, Waldrop TC. Occurrence and resolution of focal epithelial hyperplasia in two siblings with leukocyte adhesion deficiency. *J Periodontol* 1993;**64**(2):149–52.

17 Marvan E, Firth N. Focal epithelial hyperplasia in an HIV positive man. An illustrated case and review of the literature. *Aust Dent J* 1998;**43**(5):305–10.

18 Cameron JE, Hagensee ME. Oral HPV complications in HIV-infected patients. *Curr HIV/AIDS Rep* 2008;**5**(3):126–31.

19 Greenspan D, de Villiers EM, Greenspan JS *et al.* Unusual HPV types in oral warts in association with HIV infection. *J Oral Pathol* 1988;**17**(9–10):482–8.

20 King M, Reznik D, O'Daniels C. HPV-associated oral warts among HIV seropositive patients in the era of HAART: an emerging infection. *Clin Infect Dis* 2002;**34**:641–8.

21 Patton LL, McKaig R, Strauss R *et al.* Changing prevalence of oral manifestations of human immuno-deficiency virus in the era of protease inhibitor therapy. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2000;**89**(3):299–304.

22 Vilmer C, Cavelier-Balloy B, Pinquier L *et al.* Focal epithelial hyperplasia and multifocal human papillomavirus infection in an HIV-seropositive man. *J Am Acad Dermatol* 1994;**30**(3):497–8.

23 Mendez-Flores S, Esquivel-Pedraza L, Hernandez-Salazar A *et al.* Focal epithelial hyperplasia in adult patients with HIV infection: clearance with topical imiquimod. *Skinmed* 2016;**14**(5):395–7.

24 Moerman M, Danielides VG, Nousia CS *et al.* Recurrent focal epithelial hyperplasia due to HPV13 in an HIV-positive patient. *Dermatology* 2001;**203**(4):339–41.

25 Patterson AT, Andritsos L, Allen CM *et al.* Multifocal epithelial hyperplasia (Heck disease) in a patient with chronic lymphocytic leukemia. *J Cutan Pathol* 2014;**41**(8):694–6.

26 Tenore G, Palaia G, Del Vecchio A *et al.* Focal epithelial hyperplasia (Heck's disease). *Ann Stomatol* 2013;**4**(**Suppl 2**):43.

27 Viraben R, Aquilina C, Brousset P, Bazex J. Focal epithelial hyperplasia (Heck disease) associated with AIDS. *Dermatology* 1996;**193**(3):261–2.

28 Hollander CF, van Noord MJ. Focal epithelial hyperplasia: a virus-induced oral mucosal lesion in the chimpanzee. *Oral Surg Oral Med Oral Pathol* 1972;**33**(2):220–6.

29 Tate CL, Conti PA, Nero EP. Focal epithelial hyperplasia in oral mucosa of a chimpanzee. *J Am Vet Med* 1973;**163**:619–21.

30 Glad WR, Nesland JM. Focal epithelial hyperplasia of the oral mucosa in two chimpanzees (Pan troglodytes). *Am J Primatol* 1986;**10**(1):83–9.

31 Van Ranst M, Fuse A, Sobis H *et al.* A papillomavirus related to HPV type 13 in oral focal epithelial hyperplasia in the pygmy chimpanzee. *J Oral Pathol Med* 1991;**20**(7):325–31.

32 March C. Multiple papillary tumors of the labial, buccal and glossal mucous membrane. *Dental Cosmos* 1881;**23**:165.

33 Carlos R, Sedano HO. Multifocal papilloma virus epithelial hyperplasia. *Oral Surg Oral Med Oral Pathol* 1994;**77**(6):631–5.

34 Estrada L. Informe preliminar sobre algunos aspectos odontológicos de los indios Caramanta. *Bol Inst Antropol Medellin Colombia* 1956;**1**:319–21.

35 Zegarelli EV, Everett FG, Kutscher AH. Familial white folded dysplasia of the mucous membranes: an atlas of oral lesions. *Oral Surg Oral Med Oral Pathol* 1961;**14**:1436.

36 Reyes DG. Verruga de la cavidad oral. *Rev Col Med Guatemala* 1962;**13**:223–6.

37 Soncira A, Fonseca N. Sobre una lesion de la mucosa oral en los niños Indios de la Mision Los Angeles del Tokuko. *Venez Odontol* 1964;**29**:109–22.

38 Archard HO, Heck JW, Stanley HR. Focal epithelial hyperplasia: an unusual oral mucosal lesion found in Indian children. *Oral Surg Oral Med Oral Pathol* 1965;**20**(2):201–12.

39 Hettwer KJ, Rodgers MS. Focal epithelial hyperplasia (Heck's disease) in a Polynesian. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1966;**22**(4):466.

40 Decker WG, de Guzman MN. Focal epithelial hyperplasia: report of four cases in Mestizos from Cochabamba. *Bolivia Oral Surg Oral Med Oral Pathol* 1969;**27**(1):15–9.

41 Gomez A, Calle C, Arcila G, Pindborg JJ. Focal epithelial hyperplasia in a half-breed family of Colombians. *J Am Dent Assoc* 1969;**79**:663–7.

42 Praetorius-Clausen F, Willis JM. Papova virus-like particles in focal epithelial hyperplasia. *Eur J Oral Sci* 1971;**79**(3):362–5.

43 Perriman A, Uthman A. Focal epithelial hyperplasia: report of seven cases from Iraq. *Oral Surg Oral Med Oral Pathol* 1971;**31**(2): 221–5.

44 Hanks CT, Fischman SL, de Guzman MN. Focal epithelial hyperplasia. A light and electron microscopic study of one case. *Oral Surg Oral Med Oral Pathol* 1972;**33**(6):934–43.

45 Van Der Waal I, Ten Bruggenkate Chr M, Van Der Kwast WAM. Focal epithelial hyperplasia in a child from Surinam. *Int J Oral Surg* 1975;**4**(4):168–71.

46 Kuffer R, Pérol Y. Focal epithelial hyperplasia. 1st French case. Demonstration of a papovavirus by electron microscopy. *Rev Stomatol Chir Maxillofac* 1976;**77**(2):318–21.

47 Van Wyk CW, Staz J, Farman AG. Focal epithelial hyperplasia in a group of South Africans: its clinical and microscopic features. *J Oral Pathol* 1977;**6**(1):1–13.

48 Buchner A. Focal epithelial hyperplasia in Israeli families of Libyan origin. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1978;**46**(1):64–9.

49 Chen SY. Focal epithelial hyperplasia in rabbit oral mucosa. *J Oral Pathol Med* 1979;**8**(4):213–23.

50 Petzoldt D, Dennin R. Isolation of virus-like particles in a case of focal epithelial hyperplasia Heck. *Hautarzt* 1980;**31**(1): 35–6.

51 Laskaris GC, Papanicolaou SJ, Angelopoulos AP. Focal epithelial hyperplasia. The first reported case from Greece. *Dermatologica* 1981;**162**(4):254–9.

52 Lutzner M, Kuffer R, Blanchet-Bardon C, Croissant O. Different papillomaviruses as the causes of oral warts. *Arch Dermatol* 1982;**118**(6):393–9.

53 Pfister H, Hettich I, Runne U *et al.* Characterization of human papillomavirus type 13 from focal epithelial hyperplasia Heck lesions. *J Virol* 1983;**47**(2):363–6.

54 Sawyer DR, Arole G, Mosadomi A. Focal epithelial hyperplasia: report of three cases from Nigeria. *West Africa Oral Surg Oral Med Oral Pathol* 1983;**56**(2):185–9.

55 Lang E, Zabel M, Ikenberg H. Focal epithelial hyperplasia (Heck's disease): a contribution to its viral genesis. *Dtsch Med Wochenschr* 1984;**109**(46):1763–6.

56 Pilgard G. Focal epithelial hyperplasia. Report of nine cases from Sweden and review of the literature. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1984;**57**(5):540–3.

57 Moussavi S. Focal epithelial hyperplasia: report of two cases and review of literature. *J Am Dent Assoc* 1986;**113**(6):900–2.

58 Beaudenon S, Praetorius F, Kremsdorf D *et al.* A new type of human papillomavirus associated with oral focal epithelial hyperplasia. *J Invest Dermatol* 1987;**88**(2):130–5.

59 Hernandez-Jauregui P, Eriksson A, Perez R'T *et al.* Human papillomavirus type 13 DNA in focal epithelial hyperplasia among Mexicans. *Arch Virol* 1987;**93**(**1–2**):131–7.

60 Garlick JA, Taichman LB. Human papillomavirus infection of the oral mucosa. *Am J Dermatopathol* 1991;**13**:386–95.

61 Roligheđ J, Sørensen IM, Jacobsen NO, Lindeberg H. The presence of HPV types 6/11, 13, 16 and 33 in Bowenoid papulosis in an HIV-positive male, demonstrated by DNA in situ hybridization. *APMIS* 1991;**99**(**7–12**):583–5.

62 Williamson AL, Dennis SJ. The use of the polymerase chain reaction for the detection of human papillomavirus type 13. *J Virol Methods* 1991;**31**(1):57–65.

63 Chindia ML, Awange DO, Guthua SW, Mwaniki DL. Focal epithelial hyperplasia (Heck's disease) in three Kenyan girls: case reports. *East Afr Med J* 1993;**70**(9):595–6.

64 Woods KV, Shillitoe EJ, Spitz MR *et al.* Analysis of human papillomavirus DNA in oral squamous cell carcinomas. *J Oral Pathol Med* 1993;**22**(3):101–8.

65 Premoli-De-Percoco G, Cisternas JP, Ramírez JL, Galindo I. Focal epithelial hyperplasia: human-papillomavirus-induced disease with a genetic predisposition in a Venezuelan family. *Hum Genet* 1993;**91**(4):386–8.

66 Caldeira S, Dong W, Tomaklidi P *et al.* Human papillomavirus type 32 does not display in vitro transforming properties. *Virology* 2002;**301**(1):157–64.

67 Guevara A, Blondet J, Llerena V. Prevalencia y distribución de la hiperplasia epitelial focal en la población escolar de Mórrope-Lambayeque. *Perú Folia Dermatol* 2003;**14**:15.

68 Maschke J, Brauns TC, Goos M. Imiquimod for the topical treatment of focal epithelial hyperplasia (Heck disease) in a child. *JDDG J German Soc Dermatol* 2004;**2**(**10**):848–50.

69 Benevides Dos Santos PJ, Borborema Dos Santos CM, Mendonça RR *et al.* Human papillomavirus type 13 infecting the conjunctiva. *Diagn Microbiol Infect Dis* 2005;**53**(1):71–3.

70 Ledesma-Montes C, Vega-Memije E, Garcés-Ortíz M *et al.* Multifocal epithelial hyperplasia. Report of nine cases. *Med Oral, Patol Oral Cir Bucal* 2005;**10**(**5**):394–401.

71 Cuberos V, Perez J, Lopez CJ *et al.* Molecular and serological evidence of the epidemiological association of HPV 13 with focal epithelial hyperplasia: a case-control study. *J Clin Virol* 2006;**37**(1): 21–6.

72 Falaki F, Amir Chaghmaghi M, Pakfetrat A *et al.* Detection of human papilloma virus DNA in seven cases of focal epithelial hyperplasia in Iran. *J Oral Pathol Med* 2009;**38**(**10**):773–6.

73 Liu N, Wang J, Lei L *et al.* Human papillomavirus-32-associated focal epithelial hyperplasia accompanying HPV-16-positive papilloma-like lesions in oral mucosa. *J Craniofac Surg* 2013;**24**(**3**):905–8.

74 Landis MN, Lookingbill DP, Sluzevich JC. Recalcitrant plantar warts treated with recombinant quadrivalent human papillomavirus vaccine. *J Am Acad Dermatol* 2012;**67**(**2**):e73–4.

75 Khanal S, Cole ET, Joh J *et al.* Human papillomavirus detection in histologic samples of multifocal epithelial hyperplasia: a novel demographic presentation. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2015;**120**(6):733–43.

76 Hoffmann M, Schütze E, Bernhard A *et al.* Disease manifestation and viral sequences in a bonobo more than 30 years after papillomavirus infection. *Pathogens* 2019;**8**(1):13.

77 Schwartz Z, Magro C, Nuovo G. The molecular-based differentiation of Heck's disease from its mimics including oral condyloma and white sponge nevus. *Ann Diagn Pathol* 2019;**43**:151402.

78 Jayasooriya PR, Abeyratne S, Ranasinghe AW, Tilakaratne WM. Focal epithelial hyperplasia (Heck's disease): report of two cases with PCR detection of human papillomavirus DNA. *Oral Dis* 2004;**10**(4):240–3.

79 Bennett LKMD, Hinshaw MMD. Heck's disease: diagnosis and susceptibility. *Pediatr Dermatol* 2009;**26**(1):87–9.

80 Said AK, Leao JC, Fedele S, Porter SR. Focal epithelial hyperplasia - an update. *J Oral Pathol Med* 2013;**42**(6):435–42.

81 Kuhlwein A, Nasemann T, Janner M *et al.* Detection of papilloma virus in Heck's focal epithelial hyperplasia and the differential diagnosis of white-sponge nevus. *Hautarzt* 1981;**32**(12):617–21.

82 Kutcher MJ, Padilla R, Ludlow JB. Asymptomatic pebbly lesions. *J Am Dent Assoc* 2009;**140**(2):185–8.

83 Garrafa V. Alterações multiplas e benignas na mucosa bucal em indigenas brasileiros. *Caderno CEPAM* 1980;**1**:39–157.

84 Jimenez C, Correnti M, Salma N *et al.* Detection of human papillomavirus DNA in benign oral squamous epithelial lesions in Venezuela. *J Oral Pathol Med* 2001;**30**(7):385–8.

85 Ledesma-Montes C, Garcés-Ortíz M, Hernández-Guerrero JC. Clinicopathological and immunocytochemical study of multifocal epithelial hyperplasia. *J Oral Maxillofac Surg* 2007;**65**(11):2211–7.

86 Ledesma-Montes C, Mendez-Mendoza A. Unusually high incidence of multifocal epithelial hyperplasia in children of the Nahuatl population of Mexico. *Indian J Dermatol Venereol Leprol* 2017;**83**(6):663–6.

87 Matute G, Gonzalez LV, Acosta E, Restrepo MV. Prevalencia de hiperplasia epitelial focal en escolares de la comuinidad indigena de crisantia, municipio de jardin, Antioquia, 1998. *Rev Fac Odontol Univ Antioq* 1999;**11**(1):15–9.

88 Harris AMP, van Wyk CW. Heck's disease (focal epithelial hyperplasia): a longitudinal study. *Community Dent Oral Epidemiol* 1993;**21**(2):82–5.

89 Clausen FP, MØGeltoft M, Reed-Petersen B, Pindborg JJ. Focal epithelial hyperplasia of the oral mucosa in a south-west Greenlandic population. *Eur J Oral Sci* 1970;**78**(**1–4**):287–94.

90 Morency R, Laliberte H, Delamarre R. Focal epithelial hyperplasia of the buccal mucosa in a population of Cris American-Indians. *J Biol Buccale* 1981;**9**(1):95.

91 Henke RP, Guerin-Reverchon I, Milde-Langosch K *et al.* In situ detection of human papillomavirus types 13 and 32 in focal epithelial hyperplasia of the oral mucosa. *J Oral Pathol Med* 1989;**18**(7):419–21.

92 Borghelli RF, Stirparo MA, Paroni HC. Focal epithelial hyperplasia. Report of five new cases from Argentina. *Oral Surg Oral Med Oral Pathol* 1975;**40**(1):107–12.

93 Segura Saint-Gerons R, Toro Rojas M, Ceballos Salobreña A *et al.* Focal epithelial hyperplasia. A rare disease in our area. *Med Oral Patol Oral Cir Bucal* 2005;**10**(2):128–31.

94 Gonzalez-Losa MR, Suarez-Allen RE, Canul-Canche J *et al.* Multifocal epithelial hyperplasia in a community in the Mayan area of Mexico. *Int J Dermatol* 2011;**50**(3):304–9.

95 Saunders NR, Scolnik D, Rebbapragada A *et al.* Focal epithelial hyperplasia caused by human papillomavirus 13. *Pediatr Infect Dis J* 2010;**29**(6):550–2.

96 Lopez-Villanueva ME, Conde-Ferráez L, Ayora-Talavera G *et al.* Human papillomavirus 13 in a Mexican Mayan community with multifocal epithelial hyperplasia: could saliva be involved in household transmission? *Eur J Dermatol* 2011;**21**(3):396–400.

97 Artac H, Göktürk B, Bozdemir SE *et al.* Late-onset adenosine deaminase deficiency presenting with Heck's disease. *Eur J Pediatr* 2010;**169**(8):1033–6.

98 Feller L, Khammissa RA, Wood NH *et al.* Focal epithelial hyperplasia (Heck disease) related to highly active antiretroviral therapy in an HIV-seropositive child. A report of a case, and a review of the literature. *SADJ* 2010;**65**(4):172–5.

99 Syrjanen S. Human papillomavirus infections and oral tumors. *Med Microbiol Immunol* 2003;**192**(3):123–8.

100 Praetorius F, Clausen PP, Mogeltoft M. Immunohistochemical evidence of papillomavirus antigen in focal epithelial hyperplasia. *Tandlaegebladet* 1985;**89**(16):589–95.

101 Hall C, McCullough M, Angel C, Manton D. Multifocal epithelial hyperplasia: a case report of a family of Somalian descent living in Australia. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2010;**109**(1):e20–4.

102 Orfanos CE, Strunk V, Gartmann H. Focal epithelial hyperplasia of the oral mucosa: Heck's disease (author's transl). *Dermatologica* 1974;**149**(3):163–75.

103 Weidner F. Focal epithelial hyperplasia (Heck) in a Turkish family. *Hautarzt* 1996;**47**(12):927–9.

104 Kohn SR, Kohn DW. Heck's disease (focal epithelial hyperplasia). *J Am Acad Dermatol* 1980;**2**(6):533–4.

105 Steinhoff M, Metze D, Stockfleth E, Luger TA. Successful topical treatment of focal epithelial hyperplasia (Heck's disease) with interferon-beta. *Br J Dermatol* 2001;**144**(5):1067–9.

106 Akyol A, Anadolu R, Anadolu Y *et al.* Multifocal papillomavirus epithelial hyperplasia: successful treatment with CO2 laser therapy combined with interferon alpha-2b. *Int J Dermatol* 2003;**42**(9):733–5.

107 Meissner M, Pinter A, Wolter M *et al.* Multiple oral papules and plaques in a patient with Crohn's disease. *Aktuelle Derm* 2014;**40**(7):292–5.

108 Harris RJ, Rebolledo CM, Camacho CF *et al.* Trichloroacetic acid, a therapeutic option in the focal epithelial hyperplasia: presentation of a case. *Av Odontoestomatol* 2010;**26**(6):323–8.

109 Lorduy MC, Ricardo JH, Arenas YH, Carmona WM. Use of trichloroacetic acid for management of oral lesions caused by human papillomavirus. *Gen Dent* 2018;**66**(2):47–9.

110 Obalek S, Janniger C, Jablonska S *et al.* Sporadic cases of Heck disease in two Polish girls: association with human papillomavirus type 13. *Pediatr Dermatol* 1993;**10**(3):240–4.

111 Luomanen M. Oral focal epithelial hyperplasia removed with CO2 laser. *Int J Oral Maxillofac Surg* 1990;**19**(4):205–7.

112 Michael EJ, Husain S, Zalar G, Nuovo G. Focal epithelial hyperplasia in an Ecuadorian girl. *Cutis* 1999;**64**:395–6.

113 Stiefler RE, Solomon MP, Shalita AR. Heck's disease (focal epithelial hyperplasia). *J Am Acad Dermatol* 1979;**1**(6):499–502.

114 Khan IU, Ahmed M, Hakim I, Khan MM. Focal epithelial hyperplasia–a newly discovered disease in north west frontier province of Pakistan. *J Pak Med Assoc* 1992;**42**(8):189–91.

115 Guitart J, McGillis ST, Bailin PL *et al.* Human papillomavirus-induced verrucous carcinoma of the mouth—case report of an aggressive tumor. *J Dermatol Surg Oncol* 1993;**19**:875–7.

116 Nallanchakrava S, Sreebala N, Basavaraj SF. Laser excision of focal epithelial hyperplasia (Heck's disease): a rare case report. *Int J Clin Pediatr Dent* 2018;**11**(6):526–8.

117 von Elm E, Altman DG, Egger M *et al.* The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol* 2008;**61**(4):344–9.

118 Phillips H, Williams A. Focal epithelial hyperplasia : a report of a case. *Oral Surg Oral Med oral Pathol.* 1968;**26**:619.

119 Fischman SL. Focal epithelial hyperplasia. *Case reports from Paraguay and Peru. Oral Surg* 1969;**28**:389.

120 Schock RK. Familial focal epithelial hyperplasia. *Report of a case. Oral Surg* 1969;**28**:598–602.

121 Tan KN, Medak H, Cohen L, Burlakow P. Focal epithelial hyperplasia in a Mexican Indian. *Arch Dermatol* 1969;**100**:474–7.

122 Bradnum P. Focal epithelial hyperplasia (Heck's disease). *Br J Oral Surg.* 1970;**8**(2):130–2.

123 Adkins KF, Campbell AFG. Focal epithelial hyperplasia: report of a case in an Australian aborigine. *Aust Dent J* 1971;**16**: 315.

124 Gusterson BA, Greenspan JS. Multiple polypoid conditions of the oral mucosa. *Br J Oral Surg* 1974;**12**:91–5.

125 Lindeberg H. Fokal epitelial hyperplasi [focal epithelial hyperplasia]. *Nor Tannlaegeforen Tid* 1976;**86**(5):207–10. Norwegian. PMID: 1064007.

126 Starink TM, Woerdeman MJ. Focal epithelial hyperplasia of the oral mucosa. Report of two cases from the Netherlands and review of the literature. *Br J Dermatol.* 1977;**96**(4):375–80. doi: 10.1111/j.1365-2133.1977.tb07131.x. PMID: 861173.

127 Edwards MB, Hamza AE. Focal epithelial hyperplasia in Abu Dhabi. *Oral Surg Oral Med Oral Pathol.* 1978;**45**(6):902–4. doi: 10.1016/s0030-4220(78)80013-9. PMID: 277855.

128 Goodfellow A, Calvert H. Focal epithelial hyperplasia of the oral mucosa. A case report from the United Kingdom. *Br J Dermatol.* 1979;**101**(3):341–4. doi: 10.1111/j.1365-2133.1979.tb05629.x. PMID: 228693.

129 Acevedo A, Gonzales GM, Nelson JF. Focal epithelial hyperplasia. *Oral Surg Oral Med Oral Pathol.* 1981;**51**(5):524–6. doi: 10.1016/0030-4220(81)90013-x. PMID: 6941143.

130 Syrjänen S, Syrjänen K, Ikenberg H *et al.* A human papillomavirus closely related to HPV 13 found in a focal epithelial hyperplasia lesion (heck disease). *Arch Dermatol Res.* 1984;**276**(3):199–200. doi: 10.1007/BF00414020. PMID: 6089671.

131 Hallmon WW, Waldrop TC, Houston GD. Focal epithelial hyperplasia (Heck's disease). A case report. *J Periodontol.* 1985;**56**(2):89–92. doi: 10.1902/jop.1985.56.2.89. PMID: 3856655.

132 Betancourt Castro DE. Hiperplasia epithelial focal [focal epithelial hyperplasia]. *Rev Fed Odontol Colomb* 1988;**38**(165):63–8. Spanish. PMID: 2856153.

133 Jaramillo F, Rodríguez G. Multiple oral papules in a native south American girl. Focal epithelial hyperplasia (Heck's disease). *Arch Dermatol.* 1991;**127**(6):888–9, 891–2. doi: 10.1001/archderm.127.6.888. PMID: 2036039.

134 Bon A, Eichmann A, Grob R. Focal epithelial hyperplasia. *Dermatology.* 1992;**184**(4):294–5. doi: 10.1159/000247574. PMID: 1498399.

135 Chindiya ML, Awange DO, Guthua SW, Mwaniki DL. Focal epithelial hyperplasia (Heck's disease) in three Kenyan girls: case reports. *East Afr Med J.* 1993;**70**(9):595–6 PMID: 8181446.

136 Cohen PR, Hebert AA, Adler-Storthz K. Focal epithelial hyperplasia: heck disease. *Pediatr Dermatol.* 1993;**10**(3):245–51. doi: 10.1111/j.1525-1470.1993.tb00369.x. PMID: 8415301.

137 Landells ID, Prendiville JS. Oral mucosal lesions in a Somali boy. *Pediatr Dermatol.* 1994;11274–6.

138 Flaitz CM. Focal epithelial hyperplasia: a multifocal oral human papillomavirus infection. *Pediatr Dent.* 2000;**22**(2):153–4. PMID: 10769863.

139 Haisley-Royster CA, Allingham RR, Klintworth GK, Prose NS. Hereditary benign intraepithelial dyskeratosis: report of two cases with prominent oral lesions. *J Am Acad Dermatol.* 2001;**45**(4):634–6. doi: 10.1067/mjd.2001.116336. PMID: 11568764.

140 Kose O, Akar A, Safali M *et al.* Focal epithelial hyperplasia treated with interferon alpha-2a. *J Dermatolog Treat.* 2001;**12**:111–3.

141 Guill CK, Hwang LY, Iyengar V *et al.* Asymptomatic labial papules in a teenager. *Arch Dermatol.* 2002;**138**:1509–14.

142 Durso BC, Pinto JM, Jorge J Jr, Almeida OP. Extensive focal epithelial hyperplasia: case report. *J Can Dent Assoc.* 2005;**71**(10):769–71. PMID: 16324231.

143 Martins WD, de Lima AA, Vieira S. Focal epithelial hyperplasia (Heck's disease): report of a case in a girl of Brazilian Indian descent. *Int J Paediatr Dent.* 2006;**16**(1):65–8. doi: 10.1111/j.1365-263X.2006.00664.x. PMID: 16364096.

144 Binder B, Wieland U, Smolle J. Focal epithelial hyperplasia (heck disease) in a black child. *Pediatr Dermatol.* 2007;**24**(4):E31–2. doi: 10.1111/j.1525-1470.2007.00435.x. PMID: 17845152.

145 Namazi MR. Heck's disease. *Ann Saudi Med* 2007;**27**(3):222. doi: 10.5144/0256-4947.2007.222 PMID: 17568175; PMCID: PMC6077067.

146 Borborema-Santos CM, Castro MM, Santos PJB *et al.* Oral focal epithelial hyperplasia: report of five cases. *Braz Dent J.* 2006;**17**(1):79.

147 Bombeccari GP, Guzzi GP, Pallotti F, Spadari F. Focal epithelial hyperplasia: polymerase chain reaction amplification as a differential diagnosis tool. *Am J Dermatopathol.* 2009;**31**(1):98–100. doi: 10.1097/DAD.0b013e31818ffc04. PMID: 19155739.

148 dos Santos-Pinto L, Giro EM, Pansani CA *et al.* An uncommon focal epithelial hyperplasia manifestation. *J Dent Child (Chic)* 2009;**76**(3):233–6. PMID: 19941767.

149 Ricardo HJ, Lorduy CM, Caballero AD. Treatment of focal epithelial hyperplasia with trichloroacetic acid. *Rev Clin Periodontica Implantol Rehabil Oral* 2010;**5**(3):139–41.

150 De La Hera I, d Cullen R, Rivera F. Vanaclocha. Flat papulaes on the lip of a young adult. *Actas Dermosifiliogr* 2010;**101**:799–800.

151 Hashemipour MA, Shoryabi A, Adhami S, Mehrabizadeh Honarmand H. Extensive focal epithelial hyperplasia. *Arch Iran Med.* 2010;**13**(1):48–52 PMID: 20039770.

152 Gultekin SE, Tokman Yildirim B, Sarisoy S. Oral focal epithelial hyperplasia: report of 3 cases with human papillomavirus DNA sequencing analysis. *Pediatr Dent.* 2011;**33**(7):522–4 22353414.

153 Hansen. Poster 37: https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=&ved=2ahUKEwiwkO3vpJXuAhVsxTgGHQp0CdoQFjAAegQIAhAC&url=https%3A%2F%2Fwww.joms.org%2Farticle%2FS0278-2391(11)01010-X%2Fpdf&usg=AOvVaw2-MRUM6DsjavvZBg8P_g0G

154 Martinez-Escala ME, Pena MG, B ellosillo B, Vallverdu RMP. Multiple cobblestone-like papules on the inner aspect of the lip. *Ped Dermatol* 2011;**28**(4):457–8.

155 Ozden B, Gunduz K, Gunhan O, Ozden FOA. Case report of focal epithelial hyperplasia (Heck's disease) with PCR detection of human papillomavirus. *J Maxillofac Oral Surg* 2011;**10**(4):357–60. doi: 10.1007/s12663-011-0184-2 Epub 2011 Mar 3. PMID: 23204755; PMCID: PMC3267916.

156 Puriene A, Rimkevicius A, Gaigalas M. Focal epithelial hyperplasia: case report. *Stomatologija.* 2011;**13**(3):102–4. PMID: 22071419.

157 Al-Sheddi MA, Faden AA. Multifocal epithelial hyperplasia in an adult female. *Hong Kong J Dermatol Venereol* 2012;**20**: 23–7.

158 Liu N, Li Y, Zhou Y, Zeng X. Focal epithelial hyperplasia (Heck's disease) in two Chinese females. *Int J Oral Maxillofac Surg.* 2012;**41**(8):1001–4. doi: 10.1016/j.ijom.2011.10.032Epub 2011 Dec 10 22154527.

159 Ricardo HJ, Lorduy CM, Caballero AD. Treatment of focal epithelial hyperplasia with trichloroacetic acid. *Rev Clin Periodontica Implantol Rehabil Oral* 2012;**5**(3):139–41.

160 Prabhat MP, Raja Lakshmi C, Sai Madhavi N, Bhavana SM, Sarat G, Ramamohan K. Multifocal epithelial hyperplasia of oral cavity expressing HPV 16 gene: a rare entity. *Case Rep Dent.* 2013;**2013**:871306. doi: 10.1155/2013/871306. Epub 2013 Dec 24. PMID: 24455323; PMCID: PMC3884697.

161 Castro LA. Multiple flat papules on the lips of children. *Eur J Pediat Dermatol.* 2014;**24**:118–9.

162 Eshgi G, Khezrian L, Ghamsemi-Basir A, Babaee-Kiadehi. Focal epithelial hyperplasia (Heck's disease): a case report from Iran. *Iran J of Dermatol* 2014;**17**(68):76–8.

163 Galanakis A, Palaia G, Tenore G *et al.* Focal epithelial hyperplasia in a human immuno-deficiency virus patient treated with laser surgery. *World J Clin Cases* 2014;**2**(7):293–6. doi: 10.12998/wjcc.v2.i7.293 PMID: 25032206; PMCID: PMC4097158.

164 Park MW, Cho YA, Kim SM *et al.* Focal epithelial hyperplasia arising after delivery of metal-ceramic fixed dental prosthesis. *J Adv Prosthodont* 2014;**6**(6):555–8. doi: 10.4047/jap.2014.6.6.555 Epub 2014 Dec 17. PMID: 25558348; PMCID: PMC4279056.

165 Ruiz R, Silva GR, Menchaca HR. Focal epithelial hyperplasia. *Lancet.* 2014;**384**(9938):173. doi: 10.1016/S0140-6736(13)62221-7Epub 2013 Nov 22 24269109.

166 Akoglu G, Metin A, Ceylan GG *et al.* Focal epithelial hyperplasia associated with human papillomavirus 13 and common human leukocyte antigen alleles in a Turkish family. *Int J Dermatol.* 2015;**54**(2):174–8. doi: 10.1111/ijd.12538Epub 2014 Apr 16 24738569.

167 Asha D, Thomas J, Manoharan D, Satyanarayanan R. Heck's disease – a rare case report. *Biomed Pharmacol J* 2015;**8**(October Spl Edition).

168 Gemignani F, Hernández-Losa J, Ferrer B, García-Patos V. Focal epithelial hyperplasia by human papillomavirus (HPV)-32 misdiagnosed as HPV-16 and treated with combination of retinoids, imiquimod and quadrivalent HPV vaccine. *J Dermatol.* 2015;**42**(12):1172–5. doi: 10.1111/1346-8138.12967Epub 2015 Jun 5 26047065.

169 Ghalayani P, Tavakoli P, Eftekhari M, Haghighi MA. Oral focal epithelial hyperplasia: report of three cases. *Turk Patoloji Derg.* 2015;**31**(1):60–3. doi: 10.5146/tjpath.2014.01223 24585348.

170 Kubiak M, Stępień P. Focal epithelial hyperplasia (Heck's disease) – case report of a rare disease in an adult Caucasian man. *Dental and Medical Problems* 2015;**52**:516–20.

171 Mansouri Z, Bakhtiari S, Noormohamadi R. Extensive focal epithelial hyperplasia: a case report. *Iran J Pathol* 2015;**10**(4):300–5 PMID: 26351501; PMCID: PMC4539750.

172 Brehm MA, Gordon K, Firan M *et al.* Case report of focal epithelial hyperplasia (Heck's disease) with polymerase chain reaction detection of human papillomavirus 13. *Pediatr Dermatol* 2016;**33**(3):e224–5. doi: 10.1111/pde.12862 Epub 2016. Erratum in: Pediatr Dermatol. 2016 Nov;33(6):722. PMID: 27072123.

173 de Castro LA, de Castro JG, da Cruz AD *et al.* Focal epithelial hyperplasia (Heck's disease) in a 57-year-old Brazilian patient: a case report and literature review. *J Clin Med Res* 2016;**8**(4):346–50. doi: 10.14740/jocmr2466w Epub 2016. PMID: 26985258; PMCID: PMC4780501.

174 Shamloo N, Mortazavi H, Taghavi N, Baharvand M. Multifocal epithelial hyperplasia: a forgotten condition in the elderly. *Gen Dent.* 2016;**64**(5):72–4 27599286.

175 Caldeira Tinoco VL, De Souza DF, Dos Santos IAF *et al.* Focal epithelail hyperplasia (Heeks's disease): a case report. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2018;**126**(3):e57.

176 Loureiro AC, Alves LV, Venancio MAAS *et al.* Focal epithelial hyperplasia (Heck's disease): an unexpected finding. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2018;**126**(3):e128.

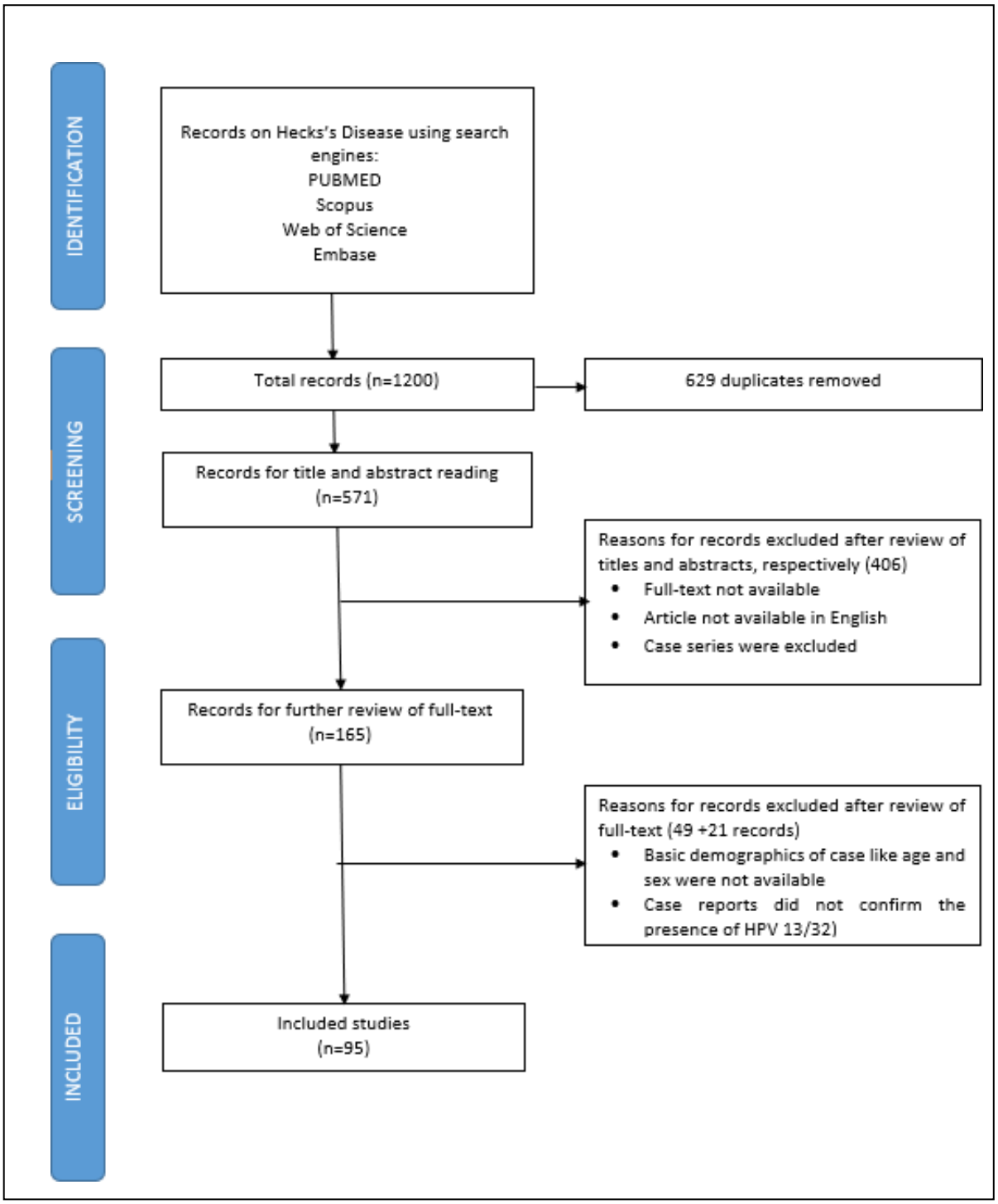
177 Do Vale DA, Ferracini LMA, Bueno MVDSR *et al.* Unusual presentation of a disseminated oral HPV infection after combined antiretroviral therapy initiation. *Rev Inst Med Trop Sao Paulo* 2019;**61**:e54.

178 Kreuter A, Silling S. Multifocal epithelial hyperplasia (heck disease) in a 7-year-old boy. *CMAJ* 2018;**190**(50):E1481. doi: 10.1503/cmaj.180882 PMID: 30559281; PMCID: PMC6291387.

End of Published Paper

7.6 SUPPLEMENTARY FILES

7.6.1: Search Strategy



7.6.2: STROBE Checklist for reporting items in observational studies of rare diseases

1. Was there an adequate description of study design and setting?

YES, if authors:
• described the method of data collection (e.g. retrospective epidemiological survey, records from a list of sources)
• described the setting (e.g. clinics, population registered at general practices, medical records database)
• relevant dates (periods for recruitment, data collection).
• give the source of denominator population for prevalence calculations (e.g. UK national statistics)

NO if authors did not report all of the above

UNCLEAR if authors reported design and setting information but it was presented unclearly or incompletely (e.g. the number of general practices was not reported or only the recruitment start date was reported)

2. Was there an adequate description of eligibility criteria?

YES, if authors:
• described inclusion criteria (exclusion criteria are not necessary)
• explicitly stated which type of MPS IV they report (specifically MPS IVA or MPS IVB)
• include enzymatic or genetic analysis as diagnoses methods (it is sufficient to state patients were enzymatically diagnosed without giving full details)

NO if authors did not report all of the above

UNCLEAR if authors
• reported eligibility criteria but it was presented unclearly (if MPS IVA is reported but no diagnostic method)
• did not clearly state which type of MPS IV was reported

3. Is the study population representative of the target population? Y, N, UNCLEAR

Note – for this question, the target population is the population studied in the study, not the population that we are studying for this systematic review. Ethnicity is not important, as long as the patient lives in the given country.

YES, if authors:
State the sources include all necessary diagnostic centres or that they have attempted to achieve full ascertainment or have outlined an extensive list of sources

NO if there is reason to believe that full ascertainment has not been achieved

UNCLEAR if we cannot be sure that all patients were included in the study (e.g. in a country multiple centres could have performed the diagnostic analyses and not all participated in the study).

4. **Is there an adequate description of outcomes?**

YES, if authors clearly describe:
• patients in denominator – live births or general population
• patients in numerator were born during study period (birth prevalence) or were living during study period (period prevalence)
• time frame of study
• the period of study e.g. 'date of first diagnosed' case to last diagnosed case or 'date of birth of first diagnosed case' to last diagnosed case

NO if authors did not report all of the above

UNCLEAR if any of the above are not clearly reported

5.Is there an adequate description of the study participants?

YES, if the authors provided more than just age (at diagnosis) and gender (for example ethnicity) then I would say the participants were adequately described

NO if authors did not report more than age and gender

UNCLEAR if the population descriptions were unclear (e.g. numbers in texts and figures didn't match or add up).

Overall score:

High – all criteria met (5 Yes's)
Medium – 1 to 2 criteria not met (i.e. 1-2 No's or Unclear)
Low – 3 or more criteria not met (i.e. ≥ 3 No's or Unclear)

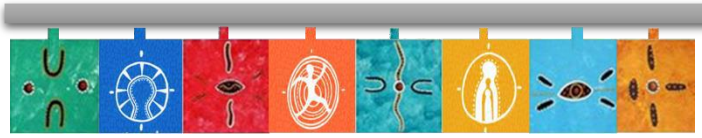
SECTION E: QUALITATIVE COMPONENT

Overview of Section E

This section contains two chapters which have a qualitative approach. Part one was associated with the barriers faced for screening and the awareness of HPV infection in Indigenous communities. The results were arranged into a socio-ecological model which addressed the problems and also provided valuable community suggested solutions. Part two involved HPV vaccinations and its perceptions amongst Indigenous peoples, which has been added as an appendix (Appendix E). The second chapter of this section evaluates the emotional response of Indigenous participants to cancer in the family and community. Both chapters are published, with the second being an invited paper from the Journal.

08

Working towards a comprehensive understanding of HPV and cervical cancer among Indigenous women: A Qualitative Systematic Review



8.1 PREFACE AND LINK TO PROJECT

The study (Study 5) presented in this Chapter is the first of two studies in this section that address the third objective of this thesis. After a preliminary search of the data, it was decided to broadly divide the research question in to two sections. The first would address understanding and awareness of HPV infection amongst Indigenous populations, and the second would focus on HPV vaccine experience and hesitancy. The first topic has been presented as Chapter 8 in this thesis, and the second is attached as Appendix E.

To the best of my knowledge, this is the first study to explore perceptions of HPV infection amongst Indigenous populations at a global level.

8.2 PUBLICATION DETAILS

This paper has been published in the British Medical Journal (OPEN) as: Sethi S, Poirier B, Canfell K, Smith M, Garvey G, Hedges J, Ju X, Jamieson LM. Working towards a comprehensive understanding of HPV and cervical cancer among Indigenous women: a qualitative systematic review. BMJ Open. 2021 Jun 30;11(6): e050113. doi: 10.1136/bmjopen-2021-050113. PMID: 34193502; PMCID: PMC8246376.

8.3 HIGHLIGHTS

- This systematic review is the first to address the qualitative characteristics of HPV infection and associated cancers among Indigenous women at a global level.
- The study highlights the continuing impact of trauma at the public policy level, providing important evidence of the work required to address health disparities that have resulted.
- The findings highlight the need for community feedback to be embedded within Indigenous health research projects so that resulting policies can be a consequence of direct Indigenous feedback.

8.4 STATEMENT OF AUTHORSHIP

Statement of Authorship

Title of Paper	Working towards a comprehensive understanding of HPV and cervical cancer among Indigenous women: A qualitative systematic review
Publication Status	☑ Published ☐ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and Unsubmitted work written in manuscript style
Publication Details	Sethi S, Poirier B, Canfell K, et al. Working towards a comprehensive understanding of HPV and cervical cancer among Indigenous women: a qualitative systematic review. BMJ Open 2021;11:e050113. doi: 10.1136/bmjopen-2021-050113

Principal Author

Name of Principal Author (Candidate)	Sneha Sethi		
Contribution to the Paper	Conceiving of Research Question Data Analysis Manuscript writing Editing and Revisions Paper submission for publication Correspondence with Editors in the publication process		
Overall percentage (%)	75%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	20/08/2021

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);
ii. permission is granted for the candidate in include the publication in the thesis; and
iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Brianna Poirier		
Contribution to the Paper	Orientation on formulation of Research Question Data Analysis Manuscript Writing Editing and Revisions		
Signature		Date	20/08/2021

Name of Co-Author	Xiangqun Ju		
Contribution to the Paper	Orientation on formulation of Research question Revision of Methodology Input in theory application Input in interpretation of results Revision of Manuscript		
Signature		Date	20/08/2021

Please cut and paste additional co-author panels here as required.

Name of Co-Author	Karen Canfell		
Contribution to the Paper	Revision of Methodology Input in theory application Input in Interpretation of Results Revison of Manuscript		
Signature		Date	20/08/2021

Name of Co-Author	Megan Smith		
Contribution to the Paper	Revision of Methodology Input in theory application Input in Interpretation of results Revision of Manuscript		
Signature		Date	17 Sep 2021

Name of Co-Author	Gail Garvey		
Contribution to the Paper	Revision of Methodology Input in theory application Input in Interpretation of Results Revison of Manuscript		
Signature		Date	20/08/2021

Name of Co-Author	Joanne Hedges		
Contribution to the Paper	Revision of Methodology Input in theory application Input in Interpretation of results Revision of Manuscript		
Signature		Date	20/08/2021

Name of Co-Author	Lisa Jamieson		
Contribution to the Paper	Orientation on formulation of Research question Revision of Methodology Input in theory application Input in Interpretation of Results Revison of Manuscript		
Signature		Date	20/08/2021

8.5 PUBLICATION

Open access Original research

BMJ Open

Working towards a comprehensive understanding of HPV and cervical cancer among Indigenous women: a qualitative systematic review

Sneha Sethi ,[1] Brianna Poirier,[1] Karen Canfell,[2] Megan Smith,[2] Gail Garvey ,[3] Joanne Hedges,[1] Xiangqun Ju ,[1] Lisa M Jamieson [1]

To cite: Sethi S, Poirier B, Canfell K, *et al*. Working towards a comprehensive understanding of HPV and cervical cancer among Indigenous women: a qualitative systematic review. *BMJ Open* 2021;**11**:e050113. doi:10.1136/bmjopen-2021-050113

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2021-050113).

Received 13 February 2021
Accepted 08 June 2021

[1]Australian Research Centre for Population Oral Health, Faculty of Health Sciences, The University of Adelaide, Adelaide, South Australia, Australia
[2]Cancer Research Division, Cancer Council New South Wales, Woolloomooloo, New South Wales, Australia
[3]Wellbeing and Preventable Chronic Diseases Division, Menzies School of Health Research Brisbane Office, Brisbane, Queensland, Australia

Correspondence to
Dr Sneha Sethi;
sneha.sethi@adelaide.edu.au

ABSTRACT

Rationale Indigenous peoples carry a disproportionate burden of infectious diseases and cancers and are over-represented among the socially disadvantaged of most countries. Human papillomavirus (HPV) is a risk factor and causative agent of cervical, oropharyngeal and other cancers. Recent literature shows evidence of Indigenous populations being at increased risk of HPV infections and its associated cancers.

Objective This is a qualitative systematic review. The objective of this study was to explore the experiences and barriers Indigenous women face in relation to HPV awareness, knowledge and cervical screening, in order to better understand factors that may mitigate against or facilitate prevention efforts for HPV infection and associated cancers.

Methods Two investigators independently searched MEDLINE, PubMed, SCOPUS and Web of Science databases (for articles published from inception until 30 June 2020) using a prespecified search strategy to identify qualitative studies on narratives of Indigenous women regarding HPV infection awareness, knowledge and cervical screening, across all geographic and income-level settings. Using a 'meta-study' approach, a social ecological model of cervical screening, infection and associated cancer prevention among Indigenous populations was formulated.

Results Five core themes were identified and formulated within the social ecological model; intrapersonal factors, interpersonal factors, institutional/organisational factors, sociocultural/community factors and public policy. These collectively formed the proposed social ecological model of HPV infection awareness and cervical cancer prevention among Indigenous women. This model has been synthesised by taking into account personal stories of Indigenous women and healthcare workers, thus offering a more nuanced, organised, structured and culturally sensitive approach to policy translation.

Conclusion The social ecological model of HPV infection awareness and cervical cancer prevention among Indigenous women offers a holistic and practical approach for Indigenous health policy makers. It clearly addresses the high risk of Indigenous populations at a global level in experience of both HPV infection and HPV-related cancers.

PROSPERO registration number CRD42020207643.

Strengths and limitations of this study

- ► This systematic review is the first to address the qualitative aspects of human papillomavirus (HPV) infection and associated cancers among Indigenous women at a global level. The review adhered to all protocols to ensure transparency and legitimacy.
- ► Another strength is the summary of community-provided solutions, in the form of personal narratives, to help decrease transmission of HPV infection and to, in turn, prevent HPV-related cancers.
- ► Our study highlights the continuing impact of trauma at the public policy level, with our findings providing important evidence of the work required to address the resulting disparities across all health indicators that have resulted from this trauma.
- ► Limitations include the decision to not include male participants, as the current statistics show a dramatic increase in the incidence of HPV associated oropharyngeal carcinoma among men.
- ► The community-identified solutions presented are mainly from one study; this demonstrates the need for community feedback to be embedded within Indigenous health research projects so that future policies can be derived from community suggestions that will have greater resonance and likely acceptance.

INTRODUCTION

Indigenous peoples, as defined by the United Nations (2004), includes all 'people with a historical continuity with pre-invasion and pre-colonial societies that developed on their territories, and who consider themselves distinct from other sectors of the societies now prevailing on those territories'. Globally, Indigenous peoples experience disproportionate health inequalities, in comparison to non-Indigenous populations, due to a unique history of colonial settlement. This has resulted in environmental dispossession of traditional lands and resources, which has negatively impacted spiritual connections

with the land and with each other.[1–4] Indigenous peoples are over-represented among the socially disadvantaged in almost every country, particularly in developed countries.[5] Public policy created by colonial settlers in many countries has been aimed at the assimilation and cultural annihilation of Indigenous peoples, resulting in mass loss of culture, language and community. Examples of assimilation policies include the Residential School System in Canada,[6] the Stolen Generations of Australia[7] and racial amalgamation in New Zealand.[8] Adelson's (2005)[9] notion of 'the embodiment of inequity', and similar works[10 11] have demanded attention be paid to the ways in which the impacts of colonial legacies, marginalisation and discrimination manifest in Indigenous peoples' health outcomes.[11] Previous works[12 13] have explored the relationship between colonisation and the intersectional nature of social determinants of health, such as race, demonstrating that healthcare patterns are rooted in historic economic, social and political circumstances and power relations.[12] This literature provides insight into the commonality of high-risk health profiles experienced by Indigenous peoples around the world and has created awareness of the need to take special measures to protect the rights of Indigenous peoples.[14 15]

Human papillomavirus (HPV) infection and associated cancers have gained significant public and research attention in recent decades. WHO has launched a three step programme for elimination of cervical cancer by 2050,[16] and the International Society for Papillomavirus Research has demonstrated support[17] for the programme with a call for equity in elimination strategies, particularly reinforcing best practices for Indigenous populations. While screening tools, such as the Papanicolaou test (Pap test), have been successful in reducing cervical cancer overall, and HPV vaccination programmes are expected to reduce rates of HPV infection and all HPV-related cancers, Indigenous communities continue to experience significantly higher rates of cervical cancer and oncogenic HPV infection compared with non-Indigenous populations.[18–22] This discrepancy in cancer is related to Indigenous women being less likely to have been screened[23–25] and compounded by implications of colonial legacies.[1–4]

It has been reported[26] that the prevalence of high-risk HPV infection related to invasive cervical cancer was 32.7% in American Indian/Alaskan Native populations in the USA compared with 24.9% in the non-Indigenous populations. A crude incidence of HPV related cervical cancer in nine Indigenous populations of the Brazilian Amazon was 46/100 000; which indicated a public health concern, also suggesting a weakness in the current secondary prevention programme.[27] Additionally, a study of three specific tribes (Aymara, Mestizo, Quechua) of Bolivian Andean women has revealed an unexpected number of cases infected with HPV.[28] The number of sexual partners was an important predictor of HPV infection in the Metit population of Canada.[29] The younger age of onset of sexual practices and less likely use of condoms has been observed in Maori tribes also.[30] A Pilaga community in Northern Argentina showed very high prevalence of HPV infection (46.7%).[31] Several reasons for not attending cervical cancer screening were described by Canadian Inuit women, including previous painful experiences and embarrassment to be examined by a male nurse.[29]

HPV-related cancers are mediated by risk factors such as sexual behaviour, tobacco use and screening participation, but these relevant health behaviours of affected Indigenous Peoples coexist within multidimensional contexts.[32 33] Bronfenbrenner's social ecological model provides a theoretical framework in which to understand the micro and macro dimensions of a phenomenon, by simultaneously considering related political, social, physical and economic environments.[34 35] Many health promotion efforts focus on individual choice, ignoring the social context of health-related behaviours. The social ecological model acknowledges the importance of the social environmental impacts on human health, beyond the ideology of individual responsibility.[35] It may be that current HPV prevention programmes are not successfully recognising and/or incorporating strategies targeted at factors beyond the individual. This is a particular shortcoming among initiatives targeting Indigenous communities who, at a global level, are much more collectivistic and group-oriented than their non-Indigenous peers.[18]

This review therefore seeks to better understand facilitators and barriers to HPV and associated cancer prevention, as experienced by Indigenous peoples on an international scale at each level of the social ecological model.[35] Combining existing literature within the framework of the model acknowledges the significance of Indigenous culture and its interaction with socioeconomic conditions.[18 35] The objective of this systematic review was to synthesise qualitative perspectives and experiences of Indigenous women and healthcare workers in the context of HPV infection, associated cervical cancer and screening methods to establish a foundation that might better facilitate targeted, holistic and culturally relevant prevention strategies.

MATERIALS AND METHODS

This systematic review has been registered in PROSPERO and the Joanna Briggs Systematic Reviews register. A prior search of the PROSPERO register revealed no similar studies. Both the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines[36] and the Enhancing Transparency in Reporting the Synthesis of Qualitative Research statement (table 1) were followed in the conduct of this systematic review.

Patient and public involvement

No patient or public involvement was undertaken in this study.

Positionality

Acknowledging that personal experiences and beliefs heavily influence research perspectives, it is critical for

Table 1 Enhancing Transparency in Reporting the Synthesis of Qualitative Research checklist

Item	Description	Reported on page #
Aim	Awareness of and barriers to HPV infection screening among Indigenous women globally	2
Synthesis methodology	Thematic content analysis guided initial data extraction for synthesis, and the social ecological model provided a theoretical framework to understand synthesised finding	4-5
Approach to searching	Pre-established search strategy which involved using terms describing the population of interest, the phenomenon we are researching as well as study designs to be included	4
Inclusion criteria	*Inclusion*: studies from inception till June 2020 were included in the study. Research based on the experiences of women of Indigenous identity or healthcare worker of Indigenous identity, personal illustrations of HPV knowledge and cervical cancer, first-person accounts; topics focused on cancers associated with HPV infection; qualitative and/or narrative, or mixed methodology; available in English; accessible via hardcopy or download; peer-reviewed *Exclusion*: research-based only on vaccination for HPV; non-Indigenous participants; only Indigenous male narratives; quantitative methodology	4
Data sources	MEDLINE, PubMed, SCOPUS and Web of Science databases; each search tailored per the design of individual database. In our search for published studies, we made use of facilities when given to run 'related' searches and the bibliography of each article was manually scanned for possible additions to the study	4
Electronic search strategy	Terms used for literature search included: 'HPV', 'Cervical cancer', 'Indigenous', 'female', 'narrative', 'story', 'qualitative', 'mixed methods'	4
Study screening methods	Two independent researchers screened studies for inclusion in the qualitative systematic review. Titles were first reviewed, then abstracts and those considered relevant by either investigator advanced to full text review	4
Study characteristic	See table 3	Table 3
Study selection results	1377 records were returned from initial search, 963 were excluded due to duplication, 24 shortlisted, 11 studies fully satisfied inclusion criteria. After appraisal, one article was removed due to lack of illustrations. 10 papers were included	Figure 1
Rationale for appraisal	Using JBI SUMARI software, articles were appraised according to the CASP (2013) method of quality appraisal	S2 and S3
Appraisal items	See S2 and S3	S2 and S3
Appraisal process	Appraisal was conducted independently by both reviewers and then findings were discussed, and consensus was required before moving forward	4
Appraisal results	One article was excluded after the appraisal because it did not satisfy inclusion criteria of personal illustrations	6
Data extraction	All text under the 'Results' and 'Conclusions' section, as well as all findings under the 'Discussion' section were analysed. Data were manually extracted with highlighters from printed versions of appraised articles and then imputed into the JBI SUMARI software	Tables 3 and 4
Software	JBI SUMARI	6
Number of reviewers	Two reviewers independently reviewed articles and extracted data. Findings were then compared, discussed and compiled	6
Coding	Data were coded from selected articles, going line by line to search for concepts and considering the author-prescribed themes	6
Study comparison	All findings were individually highlighted and written on a white board and then connections were made between findings and categories were created based on similarities within and across extracted data	6
Derivation of themes	The process of deriving themes was abductive	–

Continued

Table 1 Continued

Item	Description	Reported on page #
Quotations	Table 2	6–18, table 4
Synthesis output	Discussion and figure 2	19-20, table 4,figure 2

HPV, human papillomavirus; JBI, Joanna Briggs Institute; SUMARI, System for the Unified Management, Assessment and Review of Information.

researchers to self-situate. This review is a result of the desire to prioritise individual voices and stories of Indigenous women. After hearing first-hand accounts of various health disparities experienced by Indigenous women in South Australia, while conducting field work for a different HPV project, the primary reviewers (SS and BP) discussed the importance of the person behind a statistic and the desire to synthesise existing knowledge in HPV literature was established in order to identify future research steps. While both non-Indigenous researchers, SS is an oral pathologist with experience working with Indigenous populations in Australia and BP has qualitative experience with community-engaged scholarship in the context of Indigenous health in Canada and Australia. The supporting research team consists of Indigenous and non-Indigenous scholars with vast experience in the realm of Indigenous health research.

Identifying studies for inclusion

The reviewers used a pre-established search strategy,[37] which involved using terms (and their edited variants) describing the population of interest, the phenomenon being researched, as well as the included study designs (online supplemental file 1). Two investigators (SS and BP) independently screened the literature for eligible articles using MEDLINE, PubMed, SCOPUS and Web of Science databases from inception until June 2020. For example, the search strategy used for PubMed Database was as follows: First Nation/First Nations/Pacific Islander/Pacific Islanders/Torres Strait Islander/Torres Strait* Islanders/Aborigin*/Alaska*/Aleut*/Amerind*/American Indian/Arctic/Aymara/ Bushmen/Chukchi/Chukotka*/Circumpolar/Eskimo*/Greenland*/Hmong/Indian*/Indigen*/Inuit*/Inupiaq/Inupiat/Khanty/Maori*/Mapuche/Metis/Native*/Navaho*/Navajo*/Nenets/Quechua/Saami/Sami/Samoan*/Siberia*/Skolt/Tribal/Tribe*/Xingu*/Yup'ik/Yupik/Zuni/"African continental ancestry group"/"African continental ancestry group"/"Asian continental ancestry group"/"Health Services, Indigenous"/"Oceanic ancestry group"/"arctic regions"/"ethnic groups", "HPV", "Human Papillomavirus", "Papillomavirus", "HPV 18", "HPV*", "Qualitative", "awareness", "barriers", "screening". The search was tailored as per the design of individual databases.

In the search for published studies, the reviewers made use of facilities where the option was given to run 'related' searches, where similar studies are automatically identified. The bibliography of each article was scanned manually for possible additions to the search. The titles and abstracts were screened by both reviewers independently to assess eligibility, with those considered relevant by either investigator advancing to a full-text review. The initial search prioritised first-hand experiences, however, a number of studies included perspectives from healthcare workers that provided valuable insights into patient experiences. The decision was made to include these studies. The investigator pair fully screened articles to identify studies that fulfilled the following criteria:

- The study focused on the experiences of women and/or healthcare workers of Indigenous identity across the world.
- Findings contained personal illustrations or first-person accounts of HPV knowledge and cervical cancer screening.
- The study was qualitative or mixed methods (with clear qualitative examples).
- Where cancer was the phenomenon of interest, studies only focused on cancers associated with HPV infection (mostly cervical cancer, but did not exclude on basis of oropharyngeal cancer).
- The study was available in English.
- The study was available in hardcopy or in downloadable form.
- The study was published prior to 30 June 2020.

Exclusion criteria:

- Based only on HPV vaccination.
- Quantitative only studies.
- Studies that included narratives from men only.

While efforts were made to decrease publication bias, the reviewers recognise that limiting the search to the English language could result in loss of data in other native languages. Additionally, the inclusion of all grey literature could have provided additional findings for the study and decreased possible impacts of publication bias.

Critical appraisal

There are various validated tools for appraisal of studies; this review employed the JBI (Joanna Briggs Institute) System for the Unified Management, Assessment and Review of Information (SUMARI) critical appraisal tool[38] (online supplemental file 2). This tool includes questions regarding sample sizes, locations, methods used, techniques used and themes derived.

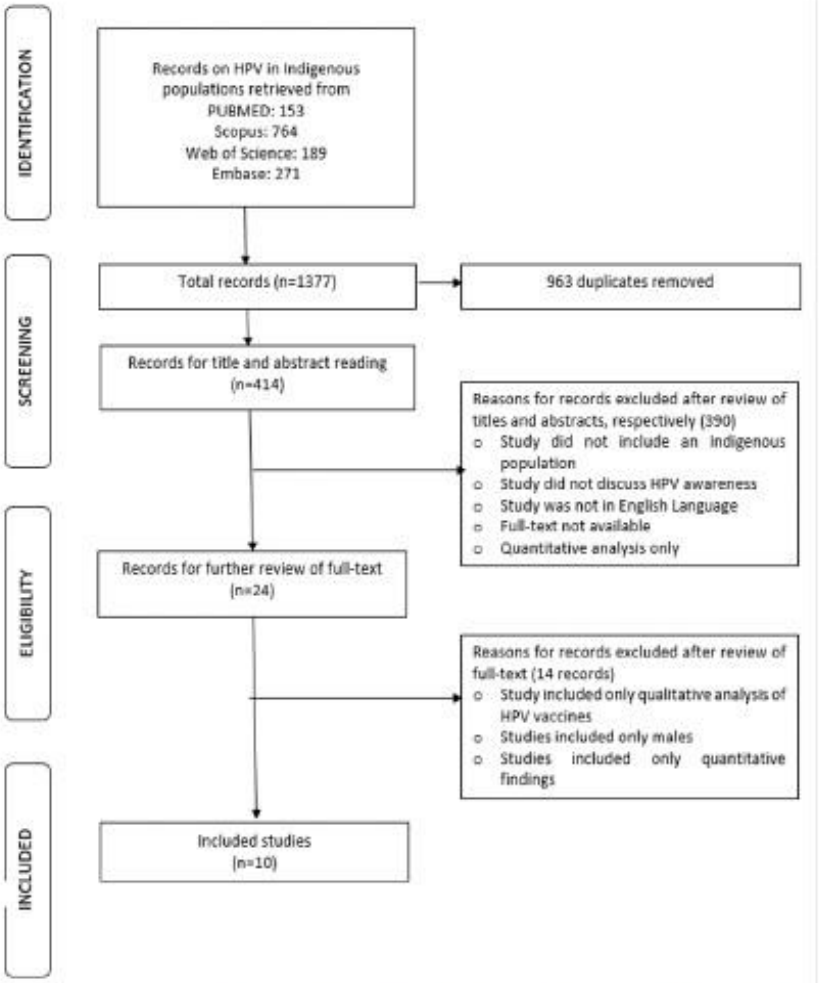


Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart for included studies. HPV, human papillomavirus.

Data extraction and synthesis

Data were extracted in two phases. For the first phase, the reviewers used concepts of thematic analysis and comprehensively identified findings from each of the included studies. These findings were extracted via a piloted extraction form and then uploaded to JBI SUMARI. The second phase used the JBI data extraction tool for all studies. Each reviewer independently scored the findings within JBI SUMARI as 'Credible (C)', 'Not Supported (NS)' and 'Unequivocal (U)'; the score for each finding was based on inter-reviewer agreement. The synthesis of findings was done manually by reviewers, which included writing all findings on a white board and identifying common phrases, themes and concepts. Common themes were grouped, with connections between other themes explored in the context of the lived experience of HPV prevention for an Indigenous woman. These categories were then transferred from the white board to the JBI SUMARI tool and each individual finding was placed within the appropriate category.

Social ecological model

On reviewing the categories and creating synthesised themes, it was apparent that findings were present at varying societal levels that are comprehensively identified in the social ecological model. The overarching themes were therefore generated to fit the social ecological model including: (1) intrapersonal factors; (2) interpersonal factors; (3) institutional and organisational factors; (4) sociocultural and community factors; (5) public policy.[34] This was additional to the solutions provided by the community which included two main themes: self-sampling and community interventions.

RESULTS

The literature search returned 1377 records, of which 963 were duplicates and consequently excluded. After being

Table 2 Inter-reviewer reliability table

Study	Questions in agreement (n)	Questions in disagreement (n)	Score
Adcock *et al*[41]	10	0	10
Allen-Leigh *et al*[40]	9	1	9
Butler *et al*[45]	10	0	10
Cerigo *et al*[42]	10	0	10
Henderson *et al*[19]	10	0	10
Maar *et al*[24]	10	0	10
O'Brien *et al*[21]	10	0	10
Tratt *et al*[43]	9	1	9
Wakewich *et al*[18]	9	1	9
Zehbe *et al*[44]	9	1	9
Mean			9.60

screened against the prespecified inclusion and exclusion criteria, 24 studies were shortlisted. Of the 24 potentially eligible studies reviewed in full, 10 fully satisfied the inclusion criteria (figure 1). The average inter-reviewer score was 9.60, indicating a very high level of agreement between reviewers (table 2). Although some studies (n=4) did not perform well according to the criteria set by the Qualitative Assessment and Review Instrument of method (online supplemental file 3) of quality appraisal,[38] the reviewers felt that studies should not be excluded on the basis of being 'less rigorous' according to one set of criteria. On the contrary, such studies were included precisely because of the richness of textual narrative provided. Other studies had minor methodological issues pertaining primarily to whether the researchers had adopted a reflexive stance by examining their own role in formulating and conducting the research.[39]

After the literature search and article appraisal, 10 studies were deemed eligible for inclusion in this review. Studies were conducted in four countries: with Māori communities in New Zealand, Aboriginal and Torres Strait Islander population in Australia, Inuit and First Nations communities in Canada, as well as Mam and Huichol communities in Mexico (table 3).

Reviewers identified 118 findings (online supplemental file 4) from the included ten studies, a chart with each finding, associated quotes and score was generated (table 4). This collaborative process resulted in 36 distinct categories, which provided an appropriate template to meta-aggregate the findings. Five main themes were synthesised by the end of this process, with reviewers in complete agreement. After completion of this process, the JBI SUMARI tool generated a meta-aggregation flowchart of all findings, categories and themes.

Intrapersonal factors

A theme strongly reflected in all included studies was intrapersonal factors. Findings revealed marginal awareness of HPV and cervical cancer, including a lack of knowledge regarding HPV symptoms and disease progression. The lack of awareness of disease progression was highlighted in more than one paper.[18 40–42] A deficiency of empathetic services was identified as a potential barrier to seeking timely health support.[41] Feelings of embarrassment and shyness were the most commonly stated experiences when visiting a doctor for screening. One study suggested that younger women feel shy, especially individuals with a history of sexual abuse,[43] while another suggested that older women are more hesitant to pursue screening options due to feeling shy.[42] Māori women have referred to this feeling as whakamā and that its tapu (a taboo) to let go of your body autonomy.[41] Feelings of vulnerability were common, and experiences of cervical screening were described as vulnerable[18]:

> I remember feeling so vulnerable, just so extremely vulnerable and, and I remember at one point he [the male physician] was talking on his phone while I was up in the stirrups and I thought uh, you know, I wonder how many other patients feel like this … There's got to be a better, kinder, gentler, more humane way to do it.

Associated with feelings of shyness were previous negative and painful healthcare experiences, which may serve to demotivate women from regular screenings. Specifically, concerns were expressed around sterilisation, empathetic procedures and rushed appointments.[40 44] Another common intrapersonal factor was fear of prognosis; for example, some participants identified this as a barrier because they feared a cancer diagnosis.[18 19 44] However, other participants found fear to be a motivator, and the desire to avoid suffering or death from this disease ensured prioritisation of prevention.[19] The financial burden associated with the Pap test and other costs including transport or childcare were substantial barriers among low-income families.[41 44] Some studies suggested that healthcare as a whole was not identified as a high priority for many individuals as stated by healthcare workers[41]:

> One in seven had not screened in ten years or more and one in six were unsure how long it had been since their last cervical screen.

Alternatively, one study suggested a deep interest and inclination towards health, where family and personal wellness were identified as motivators[45]:

> It's about listening to my body. It's about trying to keep it healthy for my children. I want to live as long as I can to bring them up to see them. Not only that, I want to feel good too. And I have had friends who have been diagnosed and that motivates me also to do it. But all in all I do it for myself and my family.

Interpersonal processes

Four of the included studies described factors at the interpersonal level.[18 19 21 45] Family relations were discussed as a way to facilitate a generational shift from an environment

Table 3 Characteristics of included studies

Study	Methods for data collection and analysis	Country	Phenomena of interest	Setting/context/ culture	Participant characteristics and sample size
Cerigo *et al*[42]	Mixed methods and focused group interviews. Thematic content analysis using NVivo software	Canada	Attitudes and experiences about cervical cancer Pap smear and HPV vaccine	Inuit women in Nunavik, Quebec	Participant characteristics: women, 31–55 years. Sample size: 6
Henderson *et al*[19]	Sharing circles (6). Analysis: NVivo	Canada	Identifying and validating known barriers and supports to HPV vaccination among First Nations people in Alberta	First Nations community leaders from Alberta	Participant characteristics: 21 females, 3 males, all First Nations Elders, health service directors and community leaders. Sample size: 24
O'Brien *et al*[21]	Ethnography, interviews. Analysis: themes and relationships among transcriptions and researcher perspectives were identified	Canada	Exploration of attitudes of beliefs of First Nations Cree women living on reserve to gain insights into how cervical screening can be better used	Community-based health centres and private locations, culture: Cree First Nations	Participant characteristics: all women, Cree First Nation. Sample size: 8
Tratt *et al*[43]	Fuzzy cognitive mapping (visual mapping) mapped and weighted participant knowledge to illustrate the impact of one on the other	Canada	Explore the possible implementation of HPV self sampling	Inuit women in Nunavik Quebec	Participant characteristics: all women over the age of 25 years. Sample size: 27
Adcock *et al*[41]	Mixed methods approach, face to face Hui, recruitment by community-based researchers. Surveys via Qualtrics Hui (focus groups, interviews) was recorded, transcribed then analysed (thematic analysis) by NVivo software	New Zealand	Potential acceptability of HPV self-sampling among Maori women who were never or under screened and also a survey of the HPV self testing among healthcare providers	Maori women and healthcare providers (both Maori and non-Maori)	Participant characteristics: Sample size: 106 (Hui), 397 (surveys)
Maar *et al*[24]	Participatory action research, mixed methods approach, semi-structured interviews. Analysis: thematic analysis	Canada	Understand the effective ways to reach First Nations women with screening information, potential or promising strategies to help motivate women to participate in cervical cancer screening and address the special issues for First Nations women with respect to cervical cancer screening	First Nations people in Northwest Ontario (Lake Superior or around Lake Nipigon)	Participant characteristics: First Nations people in Northwest Ontario (Lake Superior or around Lake Nipigon). Sample size: 70–840 members

Continued

Table 3 Continued

Study	Methods for data collection and analysis	Country	Phenomena of interest	Setting/context/ culture	Participant characteristics and sample size
Allen-Leigh *et al*[40]	9 focus groups (5–11 per group), 29 interviews, audio recordings, transcriptions and field notes taken. Analysis: two stage coding process (first level—descriptive coding; second stage—pattern codes)	Mexico (South America)	Study the barriers to use of self-sampled HPV testing and cytology among low-income Indigenous women residing in rural areas of Mexico	Mam women in Chiapas, Nahuatl women in Puebla and Huichol women in Jalisco	Participant characteristics: 20 years and above, 3 ethnic groups (Mam women in Chiapas, Nahuatl women in Puebla and Huichol Women in Jalisco). Sample size:
Wakewich *et al*[18]	Participatory action research framework, purpose sampling, traditional 'talking' circles, interviews. Analysis: open coding, NVivo software	Canada	Develop culturally sensitive approaches to cervical cancer screening and to explore the feasibility of self-sampling for HPV as an alternative screening modality to Pap cytology	First Nations women in Northwestern Ontario	Participant characteristics: healthcare workers and Elders. Sample size: 16 interviews of healthcare workers and 8 community focus groups (total 69 women)
Zehbe *et al*[44]	Data collection: field trips, teleconferences, in depth interviews, 8 focus groups, semi-structured grounded theory approach. Analysis: Nvivo 9 (QSR International)	Canada	Experiences with cancer in their community, followed by community concerns about cancer, knowledge and awareness of cervical cancer	First Nations Women, Northwest Ontario	Participant characteristics: healthcare workers—20s to 60s age groups, 15 HCPs were women and one was man. Community participants—up to 70 years age, women from First Nations identity of these, 10 women self-identified as First Nations. Sample size: 16 (interviews), 8 focus groups=total 69 women
Butler *et al*[45]	Convenience sampling yarning (followed a question guide), interpreting, listening, sharing, health questionnaire, audio recordings, transcriptions (verbatim) and field notes. Thematic analysis (NVivo)	Australia	Barriers and enablers to cervical cancer screening	Aboriginal Community Controlled Health Services or Government-run clinics that serve a large proportion of Indigenous clients—Queensland, New South Wales, Northern Territory	50 women (44 Aboriginal, 6 Torres Strait Islander), ages 25–60, 6–14 women from five different Public Healthcare Centres

HPV, human papillomavirus.

of sexual taboo to one of love and support.[18 19 21 45] Role-modelling by older family members, specifically mothers, was associated with preventive healthcare practices.[21] One mother explained the importance of talking openly about sex with her children[18]:

> Like my mother, you know, was the kind of woman that … when I first got my period, I didn't know what it was because that was something you don't talk about, your body like that. It's you know that's your personal, private, so when it happened, I had

Table 4 Illustrations from all the included studies arranged according to all the synthesised categories under each level of the socio-ecological model

Social ecological model level	Synthesised finding	Illustration
Public policy	Trauma	'They have been sexually abused, too, and I know like, in the past residential schools, that kind of thing, those people are just not comfortable because of their experiences in the past .... I will be here for a long time and whenever you need to see me, to come see me, so that even just that little thing and then when they do come I do see them, hopefully that trust builds up and I think that's a big piece with the First Nations'. (p374)[18]
		'I think one of the biggest issues um, [short pause] the barriers that prevents people from going to and maybe it's cause it's taboo is because they've been sexually abused'. (p374)[18]
		'I guess they were told about some kind of vaccine or something, like years ago, and it was something just, to try to get rid of the Native people'. (p374)[18]
		'[Residential schools] "Opened a whole can of worms; when all the illness and substance abuse went on a skyrocket"'. (p96)[19]
		'Speaking of a sister in the end-stage of cervical cancer, one middle-aged participant attributed the illness to chronic sexual abuse: "There were a couple times she had STIs [sexually transmitted infections] and didn't really know, may have been HPV or may have been another"'. (p96)[19]
		'In both sharing circles, participants argued that residential school litigation broke students' capacity for intimacy throughout their lives, playing out in self-destructive coping strategies (eg, substance dependence, early sexualization) and increased risk of victimization'. (p96)[19]
		'It must be the pesticides that are being sprayed on our cultivated land ... You can see our area and there is a layer of dust in spring and harvest'. (p96)[19]
		'Our people are starving for affection, support, respect and love'. (p96)[19]
		'The nuns make sure to remind you no matter what you do, you're going to hell'. (p96)[19]
		'We were taught to be quiet about our private parts ... a lot of sexual abuse went on, and spiritual, physical, you name it'. (p96)[19]
		'One speaker brought these lingering effects of residential schools together by describing a shift in her society from monogamous relationships to relaxed sexual boundaries, noting that with her own daughters she "didn't lay down the law like our parents did"'. (p96)[19]
		'"She got an STI because she was taken advantage of" (SC2) by someone other than her partner. The mother connected her daughter's exposure to loss of identity and heavy drinking at parties in her community. Lowered inhibitions brought on by alcohol, and illicit drug use were seen by several other speakers to have become normalized among younger generations, who "see the suffering of their parents and grandparents, and they are running to the substance abuse"'. (p96)[19]
		'In both circles, speakers expressed compassion for younger generations today: "It was a lot easier in my time because we would go to ceremonies ... but today, our grandchildren are exposed to drugs, alcohol, everything"'. (p96)[19]
		'He observed that such statistics reflect disrupted connections between partners, between Elders and youth, as well as with nature and spirituality: "We are not islands, we need to be connected to people and that is what is missing"'. (p96)[19]
		'Therefore, the burden of HPV in FN people is rooted, at least in part, in efforts by people across the lifespan to cope with the violent disruption of family and community connectedness, as well as connection to land and spirituality. This burden is manifested not only in risk-taking behaviour, but also in avoidance of wider health systems: "I think First Nations don't get checked when they are supposed to, to be honest. They just wait until it is too late to help them"'. (p97)[19]
		'Coming from a communal society, another participant observed that today many struggle "to fit into an individualistic society, and we don't fit"'. (p98)[19]
		'[When discussing child welfare] "A lot of those kids when they come back to the reserve they are very angry, there are a lot of things that happened [to them] that we don't know about"'. (p97)[19]
		'One health director who was herself FN had not approved the HPV vaccine for her own daughter, believing at the time that vaccines are perhaps "not natural, that they are more chemicals given by the government to hurt us"'. (p98)[19]

Continued

Table 4 Continued

Social ecological model level	Synthesised finding	Illustration
		'If I'm drinking and drugging, then I'm going to feel guilty about taking my children to the clinic to help them live a healthier life'. (p98)[19]
Sociocultural/ community	Gender imbalances	'The first time I went to check myself, with the Papanicolaou tests, I had problems. I got beat-up. My husband hit me because he said I had gone to do things with the [male] doctor. When it wasn't even a doctor who examined me, the [female] nurse examined me! She took the sample, but at home my husband didn't believe that'. (p4)[40]
		'I decided it [to perform the HPV test] myself, alone. I don't ask anyone's permission. … How am I going to ask him if he [her husband] wants it or not? It's not for him, it's for me'. (p4)[40]
		"Because it's a relationship thing' that implied that someone had 'cheated" (p7).[44]
		'… I know only women get cervical cancer but… they've helping it along in the same sense where they've passing it back and forth' (p7).[44]
	STI stigma	'Focus group participants were concerned that any publication of information about HPV rates on reserve could have negative effects, contributing to the stereotype that 'all native people have HPV' (FG6). As one HCP summarized: 'A lot more education has to be done about HPV and cervical cancer together' to alleviate these concerns'. (p7)[44]
		'Definitely there's always going to be a stigma about any kind of thing that's an STD [STI], because people think it's dirty or whatever. Like I've had people come in, like, even the girl I just saw with genital warts and she just couldn't believe it and couldn't like fathom who she would have got it from because everyone she's been with has only been with her. Right?'. (p373)[18]
		'Actually in the last 6 months that I've been there, I've had uh, a minimum of 5 people who have come to me who um, have been concerned about contracting STIs and did not want me writing it into their chart for fear that it would leak into the community … they're afraid of the stigma surrounding that so and a lot of times too I wasn't able to do any [cervical] screening'. (p373)[18]
		'Health centers on reserves, don't want to spread it out too much how many people have HPV. I know how the stereotype works if we pass on the information in non-native communities they will say all native people have HPV'. (p373)[18]
	Isolating effects	'it took time for one family to realize that it was "not just happening to them, it's the whole community"'. (p96)[19]
	Community support	'Yeah, just yarning with all the women, you know, getting together, having a cuppa. I think someone just bringing it up, approaching it in a way where it's just a thing where you're sitting there having a yarn about–and not feeling shame'. (p9)[45]
Institutional/ organisational	Healthcare worker cultural awareness	'Cultural awareness of healthcare workers was a major facilitator, reflected in positive patient experiences and more use of adequate communication means'. (p3)[43]
		'An additional path through which more cultural awareness could have positive impacts on the use of health services was mediated by increased confidence in patients' capabilities; thus, allowing a more active role of patient in decision-making'. (p4)[43]
		'Previous positive experiences of health personnel in their interaction with Inuit was told to be a factor that highly contributes to increase cultural awareness, countering the negative effect of a healthcare system based on non-Inuit cultural values'. (p4)[43]
		'Well, word it a way to have to do with childbearing, [which] is a sacred gift that's only given to women, let's keep our bodies healthy by getting annual check-ups, and you use some culturally appropriate like pictures, or something'. (p8)[24]
		'We need to talk to our people in a way they understand, no disrespect to any organization, but people don't look at that material [brochures], it's obvious that the way we deliver that message has to be different'. (p98)[19]
	Integrated services	'You need to make sure that you train the trainers, like teach the CHRs [community health representatives], and the women in the community that are providing service'. (p5)[24]
		'So if you're having something that they're able to come and access, [like a] sewing circle, or community kitchen, something that they're gonna get, then they'll come'. (p6)[24]
		'Well, since you're here, you know, we haven't screened for this, and when was your last Pap and what about colon cancer screening?'. (p7)[24]

Continued

Table 4 Continued

Social ecological model level	Synthesised finding	Illustration
		'If it [other STI testing] can be done on the same swab(as self-sampling), I would say, the value of that would be huge'. (p8)[24]
		'HCPs felt that education around self-testing might better be done in the context of a well woman healthcare visit, as 'part of a physical, that might get best [results]'. Women would not necessarily understand that they would still need to go to their HCP for other reproductive healthcare: 'They would, they'd probably think, well, I've had that done, so I don't need this done''. (p7)[44]
		'Eliminating multiple clinic visits was stressed'. (p5)[41]
	Negative HC experience	'I still don't know, to this day, whether they found anything or what portion they removed, if they even removed anything. I don't know! Nobody explained anything to me because, maybe because I didn't ask. Maybe they thought that I understood everything that was going on, but I didn't'. (p86)[21]
		'When you're in (western Canadian city A) and (western Canadian city B) sometimes you just get pushed along as if you're just a file. 'Here you go, this is what's wrong, this is what we're going to do, see you later.' I don't understand where I go from there, how's my health going to be affected by it now'. (p86)[21]
		'… I think it was [hospital name], and they were the roughest they could be in there. They weren't gentle at all, especially having something like that done and they say, "Lay down," and wham, you know, they're in, and that, and it was awful. I said, no, that's it'. (p9)[45]
		'Desire for bodily autonomy was often related to negative health experiences (i.e., painful pelvic examinations, inappropriate actions/comments by HCPs)'. (p3)[41]
		'We never see a doctor. The health department has to get a hold of us, the ones that are never home. There are a lot of us in the community … We hear suddenly of these workshops and information centres in the community. We wanted to go but we had other commitments so needed others to go. My niece, she died about 3 years ago because she had cancer. They brought her to Edmonton, they started her on chemo … left her kids at home'. (p97)[19]
		'One of the girls I used to visit got cervical cancer. She is very angry, she will not talk to me even though I give her support. She was told 3 years ago that she should get the tests and she didn't because she had problems for a long time'. (p97)[19]
		'She [HCP] thinks it's her(that they don't like), 'like, why is no one coming [for screening]' … 'it's not you, it took me 20 years to get to where I'm at now, and I still get people that don't trust me''. (p374)[18]
		'My doctor who I had since my oldest was born, she just up and quit, so when my next appointment, I had this guy looking at me, it's like [pause] right, so it's not like they stick around here'. (p375)[18]
	Language	'Participants reported the major importance of using visual language, ranking higher than using Inuktitut, and they stressed the communication problems behind using French or medical jargon'.(p4)[43]
		'I have a sweet little old lady, she's probably close to 80; she won't speak it, she won't speak English, she understands you, she can speak English, but she would rather speak in her own language'. (p6)[25]
	Male healthcare worker	'I had it done by a male doctor and I was uncomfortable … because of the way I was raised. My [traditional] grandmother always told me that the only man that should know you like that is your husband'. (p87)[21]
		'My first Pap smear was done by a male and I was very nervous and I just didn't want it done. Maybe that's why I didn't have another one [Pap smear] … because of that [male gender]'. (p87)[21]
		'Some people don't go [to get Pap smears], maybe they're shy … all of my friends don't go probably because they are shy or sometimes they don't want to [be] checked by a man, if it is a man that is a nurse'. (p3)[42]
	Positive healthcare experience	'My appointment was scheduled when the offices are closed so I knew he was going to be giving me some fairly bad news. The office was empty, and the lights were all turned down. It was a real comfortable surroundings. He gave me a lot of information, pamphlets, and people to phone for support'. (p85)[21]

Continued

Table 4 Continued

Social ecological model level	Synthesised finding	Illustration
		'Oh, when I have my testing done here they just make you feel so welcome and so warm, you don't feel so invaded, like a hospital … Yeah, you feel like a person, you don't seem–feel like a number'. (p11)[45]
		'The women are, you know, fairly open once they're comfortable'. (p6)[25]
		'it's all about trust and relationships, like if you can't build a relationship you're not gonna get anywhere, you might not even see them again'. (p7)[25]
	Female healthcare worker	'The girls are always looking for female doctors'. (p8)[25]
		'Feel more comfortable [with a female physician or nurse practitioner] because maybe she's going through the same thing that you're going through'. (p6)[44]
		'I only got a Pap test once and I got it from a woman … and she was trying to make me feel comfortable, but it's still really awkward'. (p6)[44]
		'… they have got the body parts as me, you know what I mean? And if they've gone through something similar to this, they'll understand what it's like … . [We have] strong cultural values on Women's Business too. And it's an invasive procedure, that's how I see it'. (p10)[45]
	Lack of results	'A lot of us say, and we've talked about this before, when we get a Papanicolaou, the results don't arrive, and we don't know what it is that's going on. There we are with the doctor, asking why the results don't arrive. … Whatever it [the result] is, they should give it to me'. (p4)[40]
		'it's crazy here, how long you have to wait for anything and half the time, you don't even get a call … you go to your next doctor's appointment for something else and [have to ask] … by the way, how about my Pap two months ago?'. (p5)[44]
	Privacy	'Health centers where staff 'phoning people, telling them, 'we've got your results … you need to make another appointment' was upsetting'. (p5)[44]
		'Especially after, you know, you finish your pap smear and then you're having lunch with them in the tea room, no thanks'. (p12)[45]
		'You know what, just sitting in the waiting room, the receptionists are phoning people telling them, we've got your results, you need an, you know, make another appointment, they say the name right out loud, they say what the test is'. (p375)[18]
		'Privacy, a small town, I mean, you can hear through the walls, you know, walls talk because there's, it's all in one building and coming in here and everybody sees the first person coming in here, they come to see me, they come to see welfare, they come to see housing, they're going and everybody knows everything'. (p375)[18]
		'Being in reserves, a lot of people know people's business and a lot of people get worried about that when you're trying to keep something personal. I mean the teddy bears talk, the leaves talk, the hydro lines talk'. (p375)[18]
	Screening convenience	'I don't know how many times they've cancelled Pap tests and [when I asked] okay well can I get it on Friday? … . [heard back] 'No, we don't do them on Friday". (p5)[44]
		'Most of us do not have doctors here … you have to drive up to [nearby town]'. (p4)[44]
		'… when I tell them it was five years, it's a five year one, they're like, "Five years, even better," knowing that they were right for five years and it picks up early, detects things earlier, they were all for it'. (p10)[45]
		'The availability of screening services outside of work hours and the potential to reduce waiting times in the clinic by having a nurse available to complete screening rather than a doctor were raised as potential solutions'. (p11)[45]
		'The size of the examination table was a concern for some women, who worried that they may not fit comfortably on the table due to having a larger body size. One woman with a physical disability stated the importance of an accessible, height-adjustable examination table that made screening more comfortable and easy for her'. (p11)[45]
		'Women were time-poor and struggled to fit screening appointments in amongst commitments to work and family, which took higher priority in women's lives'. (p11)[45]

Continued

Table 4 Continued

Social ecological model level	Synthesised finding	Illustration
Interpersonal factors	Family relations	'Well, my mother, you know, always went for her physicals; thus I learned that I was to go for my physicals … the families that do have it, you can see that progression of preventative health care'. (p5)[24]
		' … I didn't get it explained too much about that growing up into a woman off my mum. Whereas I want to do the opposite with my daughter and sort of be one step ahead of her, prepared and ready … . having that information would be good to have it there for her if she ever does want to know about it'. (p8)[45]
		'I am learning a lot in these workshops. My mother died of stomach cancer, my sister of stomach cancer. I had 5 girls, and 4 of them went through breast cancer. My oldest daughter, her cancer spread. When they were younger I made sure they all got their needles. But, you know, I have never had a workshop like this. If I get a cold, I can fight it off. When I got those needles, I was told I was able to fight the sicknesses; it won't kill you—that is what I was told. This is really good for my grandchildren; I will take this message home to my family. I have two nurses in my family, they probably know about it, but this is a really good thing I am still learning … (*speaking in Cree)*I was worried the white people would not take care of us, but they have so far [group laughs]. We need to talk to young ladies about how to take care of themselves'. (p97)[19]
		'Many of the Elders emphasized that health education within Indigenous contexts is anchored in the love and care for children. For one speaker, this affection involves "hugging your children and telling them 'I love you', you don't say goodbye to anyone"'. (p98)[19]
		'There are anti-bullying programs … and there are cultural programs; some kids are brave and some are afraid of getting immunized, but all the children support each other'. (p98) [19]
		'The best teachers are your parents'. (p98)[19]
		'I just taught them that sex isn't, it's not what you call dirty, you know, but there's a certain way you got to go about having, like for sex with a partner, you know, you got to explain that part to them, but to talk openly about sex, it's not what you call a dirty subject, yeah. If you want to know something just feel free to ask'. (p376)[18]
		'Like my mother, you know, was the kind of woman that … when I first got my period, I didn't know what it was because that was something you don't talk about, your body like that. It's you know that's your own personal, private, so when it happened, I had absolutely no knowledge what was going on in my body … And with my daughter, I didn't want her to have that feeling, so I mean, of course I changed and I explained everything but, and then that's the way things are now, women are more informed than they have been in the past'. (p376)[18]
	Intergenerational communication	'[My husband] goes and sits with the men and teaches them; for me, I can go out and explain things to the mothers and the children, and out of respect … he's getting that message across [in his sweat lodge ceremonies with men]'. (p98)[19]
Intrapersonal factors	Lack of knowledge	'The vast majority of participating women expressed the need to get screened after understanding medical facts, including but not limited to the absence of symptoms'. (p4)[43]
		'Between these two sicknesses [HPV and cervical cancer] we're in danger, we should go to the clinic or a doctor. If we feel pain in the womb, go to a doctor'. (p4)[40]
		'Well, as far as I know, the virus is transmitted through sexual contact. Then this human papillomavirus, it begins without any warning. Then later it progresses, then the discomfort in our parts [genitals] begins and that's when the discharge starts and it progresses to the cervix and when it gets to the cervix it goes into the uterus and that is when the doctor sends us for an operation'. (p4)[40]
		'Moderator: What is cervical cancer, what do you know about cervical cancer? Huichol woman 1: They say you can die of cancer, if you don't detect it early. Moderator: And how do you detect it? Huichol woman 1: With the Papanicolaou, doing it periodically. Moderator: And what's periodically? Huichol woman 1: Every three months. Moderator: Everyone, how often do you think you need to get a Papanicolaou? Huichol woman 2: Once a year. Huichol woman 3: Depends on how you feel, once a year or every two years, I get it every two years. Moderator: What do you mean, how you feel? Huichol woman 3: If you feel burning'. (p4)[40]
		'Further, we found that some women did not fully understand the purpose of the Pap smear as a method of cervical cancer screening'. (p5)[42]

Continued

Table 4 Continued

Social ecological model level	Synthesised finding	Illustration
		'A sizable proportion of the women were unable to identify a cervical cancer risk factor and were unsure if detecting cervical cancer early would affect the chance for a cure'. (p5)[42]
		'Although unintended, participants of both focus groups directed the conversation towards an educational focus due to the limited knowledge about HPV, cervical cancer and Pap smears among participants'. (p6)[42]
		'A lack of health literacy about HPV and cervical cancer and a lack of appropriate/empathetic services were also raised as barriers'. (p3)[41]
		'The health centre sent out a notification and a consent form, and they listed the benefits and risks … and I paid more attention to the risks, and I decided not to allow her to be vaccinated, because as a parent I needed to do what was best for my children'. (p98)[19]
		'These young people are lucky to get these different resources … its scary when you think about it, you didn't think about [the health risk] before, because you didn't know anything about it'. (p98)[19]
	Awareness of HPV	'Explain [what the Pap test is] then they accept the value of early diagnosis: I find that once I explain to them the importance of early detection and [that] it can be treated, they're more agreeable to [a Pap test]'. (p4)[24]
		'The biggest motivation is education, I think. You know, just teach them, let them know that the service is there, that they need to take it, it's important that they have it'. (p4)[24]
		'We know cervical cancer is 100% preventable, and I know because I read stats and see statistics that Aboriginal women are the number one on the list for dying from this'. (p5)[24]
		'If you detect it in time, you can take that sickness out so it won't progress any more and with a treatment you are fine'. (p4)[40]
		'There is a vaccine for human papillomavirus. I heard it on the radio, that there are vaccines'. (p4)[40]
	Embarrassment	'For me, I am used to getting my Pap, I'm fine with it. But for the younger girls, [or] the shy ones, [or] those who were sexually abused, they might prefer(the HPV self-sampling method)'. (p4)[43]
		'… Whatever the doctor says I just put my hand up, because after having children you don't care really. Just do what you have to do'. (p8)[45]
		'Among our population, older women reported more feelings of embarrassment than the young women'. (p5)[42]
		'Embarrassed anyway, no matter who did it'. (p6)[44]
		'Desire for bodily autonomy (retaining privacy, control over one's body) as a reason for not attending regular cervical screening—encompasses concepts of whakamā (embarrassment/shyness/reticence), tapu (sacred/taboo/forbidden)'. (p3)[41]
		'I remember feeling so vulnerable, just so extremely vulnerable and, and I remember at one point he [the male physician] was talking on his phone while I was up in the stirrups and I thought uh, you know, I wonder how many other patients feel like this … . There's got to be a better, kinder, gentler, more humane way to do it'. (p373)[18]
	Fear of prognosis	'People are scared. I'm thinking of my sister. She hasn't gone back to get retested. She did have an abnormal result the first time. I think she's afraid. Some people are afraid that if they do find cancer, it's downhill from there'. (p86)[21]
		'My fear is of having [cervical cancer] … motivates me. I want to have good health. I don't want that kind of a disease'. (p86)[21]
		'I would try and keep encouraging her … to tell her, "If they find it early they can do something about it." I try and set examples for my clients. I tell people, "Did you know this lady had this kind of cancer because she never got tested, and they could have done something about it right away and she would still be here"'. (p86)[21]
		'HPV, like, whoa, I don't have that, like, I don't even want to know if I have that'. (p7)[44]
		'Once they corrected the cervical cancer you would end up with cancer somewhere else'. (p96)[19]
	Financial barriers	'If the van was full, [you would] have to get a ride … some of us don't have cars, you know'. (p5)[44]

Continued

Table 4 Continued

Social ecological model level	Synthesised finding	Illustration
		'Women with children and work commitments also had difficulty arranging childcare and time off work to keep their appointments. As a HCP commented: 'it certainly does pose challenges with regards to babysitting care and the mother being away for an entire day". (p5)[44]
		'Older women were more likely to mention a previous bad experience and were less likely than younger women to mention cost or other financial barriers. Opinions varied about cost being a barrier (as many clinics offer free cervical screening). Some highlighted hidden costs (transport, parking, childcare)'. (p3)[41]
	Healthcare priority	'One in seven had not screened in ten years or more and one in six were[41] unsure how long it had been since their last cervical screen'. (p2)[41]
		'it's about listening to my body. it's about trying to keep it healthy for my children. I want to live as long as I can to bring them up to see them. Not only that, I want to feel good too. And I have had friends who have been diagnosed and that motivates me also to do it. But all in all I do it for myself and my family'. (p6)[45]
		'… it's no shame, you have to go and do your tests and all that … Every women [sic] in Australia have to do it every time, black or white … I don't get shame, because I want to look after myself and for my health too'. (p8)[45]
		'it's just what you do. I brush my teeth. it keeps coming down to that because it really for me is just about general body maintenance, you brush your teeth, you eat your food, I take my tablets … I do what I have to do'. (p6)[45]
		'I'll always remember that lady, and she was so nice too. And she's going, your job now is mummy, and you've got to be here, have this test every two years. And because that was at my six week check-up and I didn't want to have the pap smear, and she's going, you don't want to leave him. And I'm thinking, oh my God, because I was a single mother, oh my God, I've got to look after him. So I did; never missed it'. (p9)[45]
	Pain	'[When they did the Papanicolaou test], maybe they did it wrong. I don't know, but I felt something like a scrape. Then I thought maybe the equipment wasn't disinfected. … I thought about it a lot before doing it again, because I was afraid'. (p4)[40]
		'The Pap is uncomfortable but it has to be done'. (p5)[44]
		'it doesn't get any easier, like the first time and then the next year, it didn't get any easier for me'. (p5)[44]
		'I didn't like the way it felt, that's why I didn't want to go back there'. (p5)[44]
		'They don't want their Paps [be]cause it hurt'. (p5)[44]
		'The test also could be exceptionally painful if providers were 'in a rush' or 'rough' and did the procedure 'real quick"'. (p5)[44]
		'Some women, when they come to the appointment, they decide they don't want to get a Pap, because it's uncomfortable, they're just afraid'. (p5)[44]
Solutions—self sampling	Convenience	'Informant #14: I think that's the best idea that has come out of anything, like it's not invasive, you do it in your own home, at your own time … I.Z.: Whenever you, you know, are ready for it and … Informant #14 I think that with education along with it that this is what it is, I think that the success rate will be phenomenal with it because it's in their own home'. (p8).[24]
		'it is more comfortable to do it at home … It's simple'. (p6)[44]
		'I think the self-test is beneficial for them all because sometimes people don't have time for appointments to take off work, it [the Pap] is kind of an inconvenience'. (p6)[44]
		'Even hearing(about self-testing), people are just, What? Oh, I'd do that, for sure, instead of me going to the doctor'. (p6)[44]
		'Doing a self-test doesn't take very long … it's something that can be dealt with, done, gone'. (p6)[44]
		'I think more people would monitor it that way and test it themselves, like 'well maybe not today, but … eventually I'm going to try it'. (p6)[44]
		'… I think the prevalence(participation in self-testing)rate would go up'. (p5)[44]
		'Women wouldn't be so agitated and nervous about having the(self-)test'. (p5)[44]

Continued

Table 4 Continued

Social ecological model level	Synthesised finding	Illustration
		'With participants using terms such as 'easier', 'more comfortable', 'less intrusive' and 'brilliant'(to describe self-testing)'. (p3)[41]
		'Participants discussed the value of providing multiple options and flexibility to cater to diverse populations, such as through community outreach services, was suggested for optimum engagement'. (p5)[41]
		'it's simple, it's not like you are having forceps in you'. (p376)[18]
	Decreased pain	'Well, this one(the self-sampled HPV test)is better, because it is more comfortable to do it'. (p5)[40]
	Education	'If you hand me a kit, I won't touch it. Because I wouldn't know what to do, what if I did it wrong, or whatever, right, so? And I think a lot of people would be that way'. (p7)[44]
		'You just give a test kit to them at home, the majority of them are just going to throw them out'. (p7)[44]
		'HCPs agreed that with appropriate support and education, HPV self-testing will benefit never/under-screened Māori'. (p4)[41]
		'Most frequently [participants] said they would be happy to do the HPV self-test in a clinic or their own home, and emphasised having good support and education to increase their confidence about properly doing it'. (p5)[41]
	Privacy	'Would feel more comfortable with that(self-test)than a male doctor'. (p6)[44]
		'Self-testing would also address the 'trust issues' that discouraged women from seeking care from non-Indigenous HCPs'. (p6)[44]
		'it's a lot less clinical … stripping down and allowing someone else to do the scraping of the cervix, the whole uncomfortable procedure of going through a Pap opposed to doing it privately in the bathroom on your own is a huge difference'. (p5)[44]
		'A lot more private, at home, if you do it by yourself'. (p5)[44]
		'Women would prefer to be discreet, do it themselves and get their own results and not have their results shared with others'. (p5)[44]
	Autonomy	'I really strongly believe that … because I was the one that was doing it(self-sampling), I was the one that was in control … and this way it gave me the ability to do it myself and I got all the results, they were fine; … it was also self-empowering, great, I like that'. (p6) [44]
		'Option of taking it home might make women "feel more empowered" and contribute to a better relationship with HCPs'. (p6)[44]
		'Think it(self-sampling)would be, I think it would be great, because it provides them with some autonomy and allows them to take control of the situation. That would be really great actually … . I think it would increase [education opportunities] actually, yup, because it's a lot less clinical right, cause like you say, it's a lot less you know, stripping down and you know, allowing someone else to do the scraping of the cervix, you know, the whole uncomfortable procedure of going through a Pap opposed to doing it privately in the bathroom on your own is a huge difference'. (p376)[18]
	Decreased embarrassment	'This one [the HPV test] is good because it [cytology or the Papanicolaou test] really does embarrass you, not because your husband doesn't want it or doesn't let us, but because it's embarrassing and because of embarrassment we don't do it, and so this(self-sampled HPV test)is good for us'. (p5)[40]
		'Because you do it yourself, since always, even if there is trust, you feel a little embarrassed to undress in front of someone else'. (p5)[40]
		'I think it(self-sampling)would definitely be more private … They wouldn't be so embarrassed … all kinds of people are easily embarrassed'. (p376)[18]
Solutions—community level	Informal community communication	'Workshops, information sessions: I have lunch and learns. That's a start. There's all different venues bringing that into the community'. (p5)[24]
		'I would concentrate on a day that's important to the women, like Mother's Day. The mothers would all come and the grandmas would come and the aunts would come. I would have guest speakers come in as well and there would be a dinner, a luncheon, or a feast of some sort. I would bring somebody in who had a little bit of charisma like a Tai Chi instructor who cooks meals'. (p6)[24]

Continued

Table 4 Continued

Social ecological model level	Synthesised finding	Illustration
		'For our little group of work girls, [the] service team, we always tend to remind each other as well, like, 'Hey, is it time for your check-up yet, like?". (p7)[24]
		'I think it's just sort of word of mouth, spreading things around, and just kind of bringing it up, you know, all the time'. (p7)[24]
		'I call four people and then each one of the people I call, they call four people and it's something that we're trying to work on'. (p7)[24]
	Humour	'We didn't specifically talk about HPV, but we talked about STDs [during the education session]. Yeah, I think they got it because they still, when they see me on the streets here, we kind of giggle about it because we used bananas [for the sex education], you know, and they'll ask me: "Are you bringing bananas next week?" You know, so, it was a fun thing'. (p6) [24]
	Incentives	'It's hard to get people coming unless we have food and incentives'. (p6)[24]
	School education	'Start early, in school already: we should get our younger girls out there, and have that part as [education], at [grade] 8, and I know they're doing great in the school, getting it out there, about STDs'. (p5)[24]
	Social media	'You could even [do] something as simple as Facebook. Everybody's on Facebook'. (p5)[24]
	Survivor stories	'I think if there was someone just sharing stories. If a woman was willing to share her story that she's had this and got screened early. Girls like to listen to things like that, and the women like to listen to things like that. I beat this and I did that. Something like that would motivate them'. (p5)[24]
	Positive inspiration	'… and being a health worker too because then I can say, "No, I do mine," … it feels a bit shame but you can talk to your patient and encourage them to do it because you've done it and if I hadn't done it, well, I shouldn't be saying those things to the patient'. (p12)[45]

absolutely no knowledge what was going on in my body … And with my daughter I didn't want her to have that feeling, so I mean, of course I changed and I explained everything.

Intergenerational communication was also identified as important for educating children and as a critical aspect of cultural traditions[19]

> [My husband] goes and sits with the men and teaches them; for me, I can go out and explain things to the mothers and the children and out of respect … he's getting that message across [in his sweat lodge ceremonies with men].

Institutional/organisational factors

All of the included studies discussed factors at the institutional/organisational level that impacted cervical screening. Some items such as cultural awareness among healthcare workers, integrated services, female healthcare workers for screening and positive healthcare experiences were discussed as facilitators for screening. However, other institutional aspects such as negative healthcare experiences, language barriers, male healthcare workers for screening, lack of results, privacy concerns and screening availability were identified as barriers to screening. Both participants and healthcare workers suggested integrated services (Pap smears combined with other services) as a way to eliminate multiple clinic visits.[21 41 44] Offering services in local languages, eliminating medical jargon[21 45] and incorporating holistic healthcare approaches were identified as potential facilitators. Geographically remote communities described difficulties associated with building trusting relationships at healthcare centres, due to a high turnover of healthcare workers.[18] Discussions of the gender of the healthcare worker performing screening services (such as a Pap) elicited strong responses, with male healthcare workers identified as a barrier[19 42] and female healthcare workers as a facilitator.[21 44 45] Especially in smaller communities, lack of privacy was a substantial concern that impacted decisions to access healthcare services,[18 44] as evident in the following quote[18]:

> Being in reserves, a lot of people know people's business and a lot of people get worried about that when you're trying to keep something personal. I mean the teddy bears talk, the leaves talk, the hydro lines talk.

Lack of communication about results and lack of screening availability[40 44 45] were highlighted as obstacles to accessing services; many participants expressed a desire to receive results regardless of negative or positive outcomes. Positive healthcare experiences enticed regular utilisation of services,[19 21] while negative healthcare experiences impeded the use of services.[18 19 41] Specifically, participants felt that often procedures were not fully explained,[18 19] which competed with a desire for body autonomy. The frustration of this experience was felt by many participants, as shown in the following quotation[19]:

> I still don't know, to this day, whether they found anything or what portion they removed, if they even removed anything. I don't know! Nobody explained anything to me because, maybe because I didn't ask. Maybe they thought that I understood everything that was going on, but I didn't.

Sociocultural/community

This theme was separated into 5 categories, with key quotes arising from 6 of the 10 included studies. Gender imbalances highlighted male dominance in communities, and the consequential inequalities based on gender. Male tendencies towards promiscuity were considered to be a contributing factor for bringing HPV into the home, which affected screening practices due to the associated stigma of an unfaithful partner.[44] Religious and cultural beliefs prevented many women from attending cervical screening and/or treatment. Women shared their experiences of violence and a general disregard for their health by their male partners[40]:

> The first time I went to check myself, with the Papanicolaou tests, I had problems. I got beat-up. My husband hit me because he said I had gone to do things with the [male] doctor. When it wasn't even a doctor who examined me, the [female] nurse examined me! She took the sample, but at home my husband didn't believe that.

One healthcare worker indicated an urgent need for education to alleviate the negative concerns and sense of humiliation associated with cervical screening.[44] Healthcare workers in one study described patient requests to not document diagnoses and feelings of nervousness around potential breaches of confidentiality in the community[18]:

> Actually in the last 6 months that I've been there, I've had uh, a minimum of 5 people who have come to me who um, have been concerned about contracting STIs and did not want me writing it into their chart for fear that it would leak into the community … they're afraid of the stigma surrounding that so and a lot of times too I wasn't able to do any [cervical] screening

Participants frequently described a fear of disappointing community and family; that sense of shame and humiliation was a prime concern and barrier to regular screening.[43] Discussing the isolating effects of a cervical cancer diagnosis, one study reflected on how the diagnosis of a single person is the suffering of not one individual but an entire community.[18]

Public policy

While participants in the included studies tended to focus on discussions of institutional/organisational and intrapersonal factors, two of the Canadian studies[18 19] highlighted the impact of traumatic experiences on accessing screening services. Specifically, the sexual abuse experienced at government-mandated residential schools in Canada has created an environment of sexual taboo where health concerns are not discussed, and services are not sought. This sentiment is illustrated by the following quotation[18]:

> They have been sexually abused, too, and I know like, in the past residential schools, that kind of thing, those people are just not comfortable because of their experiences in the past.

A lack of community connection and relationships was discussed as a consequence of the sexual abuse experienced in residential schools, and substance-dependence was identified as a coping mechanism.[18] Intergenerational trauma and child removal were also mentioned as barriers to accessing health services, both of which are a result of government-mandated public policies.[46]

Solutions

Many participants identified solutions to the aforementioned obstacles which were categorised at each level of the social ecological model. Self-sampling[18 21 40 41] and community-level initiatives[21] were discussed as potential ways forward to address some of the concerns and common experiences shared across all included studies. The idea of self-sampling was associated with increased convenience,[18 21 41 44] privacy[44] and autonomy[18 44] as well as reduced embarrassment[18 40] and pain.[40] The need for education prior to self-sampling was stressed as a means to ensure a sound understanding and completion of tests.[41 44] The potential increase in perceived bodily autonomy increased the acceptance of self-sampling[44]:

> I really strongly believe that … because I was the one that was doing it [self-sampling], I was the one that was in control … and this way it gave me the ability to do it myself and I got all the results, they were fine; … it was also self-empowering, great, I like that.

Maar *et al* discussed a variety of community-level tactics to increase engagement and a desire to seek out and use healthcare services.[24] Informal community communication at events as well as by word of mouth was seen as valuable. Integrating HPV screening with female-oriented celebrations and workshops was discussed as a way to support screening behaviours. Use of school education, survivor stories, social media, incentives and humour were all identified as potential pathways to increasing screening participation. One healthcare worker described how she used humour in an educational workshop[24]:

> We didn't specifically talk about HPV, but we talked about STDs. Yeah I think they got it because they still, when they see me on the streets here, we kind of giggle about it because we used bananas [for the sex education], you know, and they'll ask me: 'Are you bringing bananas next week?' You know, so it was a fun thing.

Sethi S, *et al*. *BMJ Open* 2021;**11**:e050113. doi:10.1136/bmjopen-2021-050113

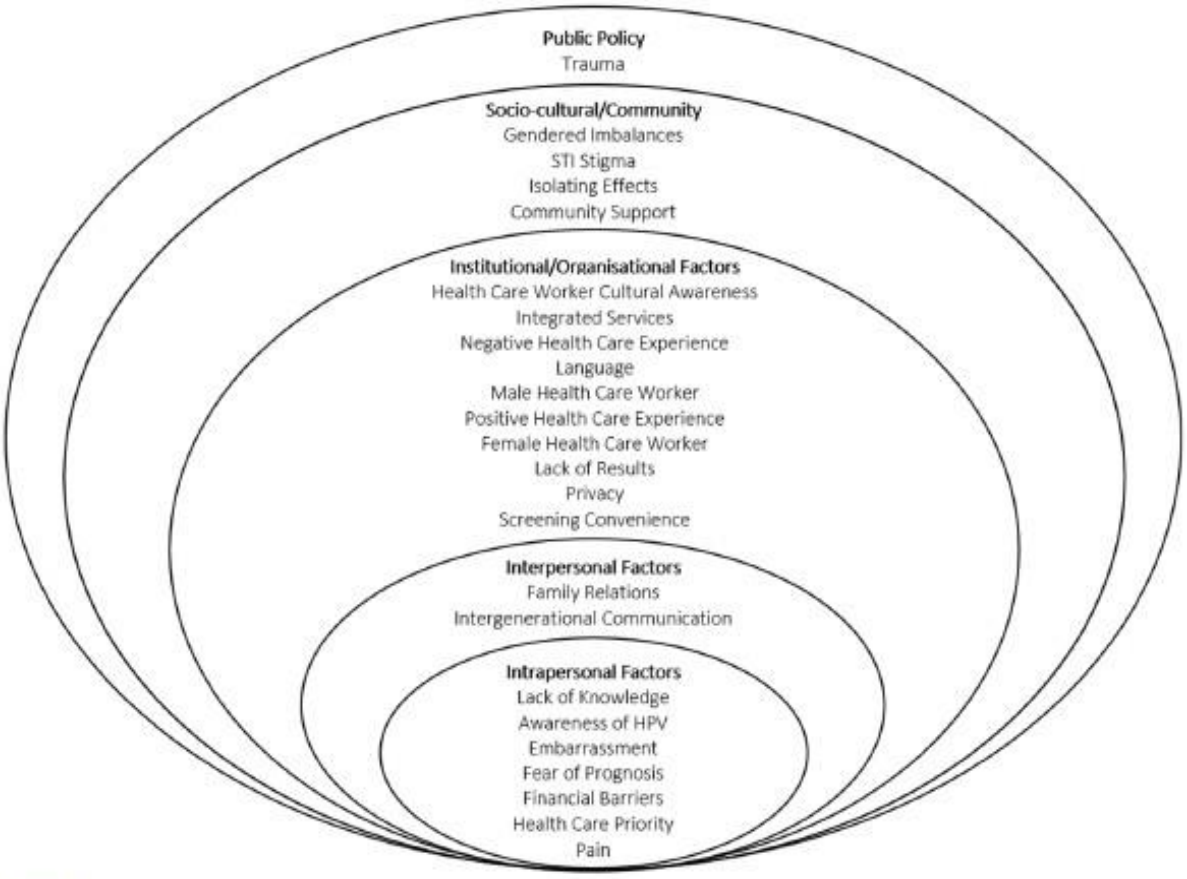


Figure 2 Socio-ecological model. HPV, human papillomavirus; STI, sexually transmitted infection.

Social ecological model

Two studies explored experiences relevant on all five levels of the social ecological model. All included studies addressed issues on at least two levels of the model (figure 2). Five studies incorporated themes or frameworks that focused exclusively on two ecological levels. All studies discussed factors at the institutional and intrapersonal level, while two studies focused primarily on themes related to public policies. The distribution of themes proposed at each ecological level of the model, according to all included studies is included in table 5.

Table 5 Social ecological model distribution of studies

Studies	Public policy	Sociocultural/ community factors	Institutional/ organisational factors	Interpersonal factors	Intrapersonal factors
Adcock *et al*[41]			■		■
Allen-Leigh *et al*[40]		■			■
Cerigo *et al*[42]			■		■
Henderson *et al*[19]	■	■	■	■	■
Maar *et al*[24]			■	■	■
O'Brien*et al*[21]			■		■
Tratt *et al*[43]			■		■
Wakewich *et al*[18]	■	■	■	■	■
Zehbe *et al*[44]			■		■
Butler *et al*[45]		■	■	■	■

Highlighted boxes show the contribution of a study to a particular ecological level.

DISCUSSION

The aim of this systematic review was to collate the experiences of Indigenous women and healthcare workers with regards to HPV, associated cancers and screening methods. A secondary aim was to generate an understanding to inform future HPV prevention strategies. By mapping findings within the social ecological model levels, this review highlights gaps in current HPV practices and identifies areas to be addressed based on first-hand experiences.

The first level of the social ecological model included factors at an intrapersonal level. Lack of knowledge and awareness of HPV infection and its risks persisted in the context of other priorities taking precedence over routine health checks. Two prominent barriers were expressed in all papers: financial burdens and feelings of embarrassment. These factors affect an individual's personal decision to seek screening or preventive healthcare services.

The level of interpersonal factors revolved around two main concepts of family relations and intergenerational communication. The communication within one family unit, from parents to children and even the openness of children with their parents, around discussions involving sexual behaviour and practices was taboo. A greater emphasis on, and openness to, education across the life course could increase the acceptability of screening. A lack of intergenerational communication was identified as a potential predisposing factor to higher risk sexual behaviours.

The third level of the social ecological model, institutional/organisational, had nine synthesised findings that demonstrated how positive and negative healthcare experiences impact current perceptions towards screening and HPV infection. There was an emphasis on lack of empathy by some healthcare workers (doctors, nurses, etc) while screening and dealing with sensitive procedures. A preference of being attended to by female healthcare workers, especially for cervical smears and examination, was observed. Worry due to lack of results after the tests was common, and often was interpreted as bad news which had an impact on participant's daily life and mental health.

The fourth level, sociocultural/community, includes factors that affect HPV-associated cancer prevention and awareness at a community level. This level included discrimination on the basis of gender and highlights male dominance that exists in some communities. This level also examined the stigma and shame of being diagnosed with a sexually transmitted infection and a common fear of being seen at the doctor's office. The experience of isolation faced after diagnosis/treatment is also a common barrier that impedes regular screening.

The results of the systematic review found trauma as the single synthesised finding at the social ecological model level of public policy. Personal quotes revealed the impacts of sexual abuse, physical abuse, drug abuse and traumatic ancestral experiences which continue to have an intergenerational impact across families and communities. Findings revealed a general mistrust towards the health system and healthcare workers. These findings highlight the urgent need to begin building trust between Indigenous communities and local health services in the provision of culturally safe care. Increased trust could help increase the acceptability of current prevention programmes and treatment solutions.

In addition to the themes of the social ecological model, the theme of self-sampling was prominent in most papers. Self-sampling is a solution which may provide more control, independence, privacy and convenience, and in turn increase screening participation. Community-identified solutions included the use of local survivor stories, which were thought to provide strength and courage to other community members to attend regular cervical cancer screenings and to not fear the diagnosis or to overcome the fear by taking preventative steps. The use of humour and social media were both innovative and socially acceptable solutions for creating awareness and educating community members with contemporary knowledge of HPV infection and its effects.

Strengths and limitations

To the best of our knowledge, this systematic review is the first to address the qualitative aspects of HPV infection and associated cancers among Indigenous women at a global level. The review adhered to all protocols to ensure transparency and legitimacy. Another strength is the summary of community-provided solutions, in the form of personal narratives, to help decrease transmission of HPV infection and to, in turn, prevent HPV-related cancers. An innovative strength of this study is the inclusion of the social ecological model as a theoretical framework. This model enables conceptualisation of a more holistic approach to HPV prevention for Indigenous women at a global level. In accordance with other studies, our study highlighted the continuing impact of trauma at the public policy level, with our findings providing important evidence of the work required to address the resulting disparities across all health indicators that have resulted from this trauma.[46–48]

Limitations include the decision to not include male participants, as the current statistics show a dramatic increase in the incidence of HPV-associated oropharyngeal carcinoma among men.[49] Additionally, the majority of articles are from Canada. This highlights the need for more research focusing on Indigenous perspectives and experiences regarding HPV screening and diagnosis in other countries. The community-identified solutions presented are mainly from one study. There is a lack of embedded community feedback in the studies included in this review despite the well-documented importance of community suggestions in improving the acceptability and success of Indigenous health programmes. Future policies and initiatives should prioritise Indigenous voices through incorporation of community suggestions.

CONCLUSION

Qualitative systematic reviews are increasing in the literature. They have particular utility in informing policy decisions, as the success of any new policy or intervention depends on its acceptance of, and sustainability in, a given population. While quantitative studies provide clarity with respect to disease spread or burden of a health condition, qualitative studies play a significant role in the management and generation of possible solutions to that health condition/disease. The social ecological model has a structured, multi-level approach with sociological, behavioural and individual aspects. Future research needs to expand the geographical scope of the current work, beyond Canada, and integrate community-identified solutions. Policies around HPV screening and diagnosis for Indigenous communities, globally, need to prioritise a holistic approach to healthcare, addressing barriers and facilitators at each level of the social ecological model, and prioritising specific community needs.

Contributors SS, BP and JH conceived the presented idea. SS, BP, XJ, LMJ developed the theory and performed the data collection. MS, KC, GG verified the analytical methods. JH encouraged SS and BP to explore the cultural limitations and beliefs leading to inaccessibility of cervical cancer screening. MS, KC, GG and LMJ supervised the work. SS and BP primarily wrote the manuscript under the supervision of GG, MS, KC, LMJ and XJ. All the authors discussed the results and contributed to the final manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information. All data relevant to the study are included in the article or uploaded as supplementary information.

ORCID iDs

Sneha Sethi http://orcid.org/0000-0002-3571-5298
Gail Garvey http://orcid.org/0000-0001-5065-5716
Xiangqun Ju http://orcid.org/0000-0003-4759-3918
Lisa M Jamieson http://orcid.org/0000-0001-9839-9280

REFERENCES

1 Axelsson P, Kukutai T, Kippen R. The field of Indigenous health and the role of colonisation and history. J Popul Res 2016;33:1–7.
2 Paradies Y. Colonisation, racism and Indigenous health. J Popul Res 2016;33:83–96.
3 Richmond CAM, Ross NA. The determinants of first nation and Inuit health: a critical population health approach. Health Place 2009;15:403–11.
4 Valeggia CR, Snodgrass JJ. Health of Indigenous peoples. Annu Rev Anthropol 2015;44:117–35.
5 Gracey M, King M. Indigenous health part 1: determinants and disease patterns. Lancet 2009;374:65–75.
6 Bombay A, Matheson K, Anisman H. The intergenerational effects of Indian residential schools: implications for the concept of historical trauma. Transcult Psychiatry 2014;51:320–38.
7 Rigney LI. Native title, the stolen generation and reconciliation. Interventions 1998;1:125–30.
8 Williams DV. The continuing impact of amalgamation, assimilation and integration policies. J R Soc N Z 2019;49:34–47.
9 Adelson N. The embodiment of inequity: health disparities in Aboriginal Canada. *Can J Public Health* 2005;96 Suppl 2:S45–61.
10 Sa T, J P, K P. Assimilation and acculturation in native Hawaiian and other Pacific Islander (NHOPI) health and well-being. POJ Nurs Prac Res 2020;4:1–5.10.32648/2577-9516/4/1/1
11 Allan B, Smylie J. First peoples, second class treatment: the role of racism in the health and well-being of Indigenous peoples in Canada. Toronto: Wellesley Institute, 2015.
12 Bourassa C, McKay-McNabb K. Racism, Sexism and Colonialism: The Impact on the Health of Aboriginal Women. In: Canadian woman studies: an introductory reader. Toronto: Inanna Publications, 2006: 540–51.
13 Browne AJ, Smye VL, Varcoe C. The relevance of postcolonial theoretical perspectives to research in Aboriginal health. Can J Nurs Res 2005;37:16–37.
14 Leeuw Sde, Maurice S, Holyk T. With reserves: colonial geographies and first nations health. Annals of the Association of American Geographers 2012;102:904–11.
15 UN. Indigenous peoples at the United nations. Available: https://www.un.org/development/desa/indigenouspeoples/about-us.html
16 World Health Organization. World health assembly adopts global strategy to accelerate cervical cancer elimination, 2020. Available: https://www.who.int/news/item/19-08-2020-world-health-assembly-adopts-global-strategy-to-accelerate-cervical-cancer-elimination
17 Lawton B, Heffernan M, Wurtak G, *et al*. IPVS policy statement addressing the burden of HPV disease for Indigenous peoples. Papillomavirus Res 2020;9:100191.
18 Wakewich P, Wood B, Davey C, *et al*. Colonial legacy and the experience of first nations women in cervical cancer screening: a Canadian multi-community study. Crit Public Health 2016;26:368–80.
19 Henderson RI, Shea-Budgell M, Healy C, *et al*. First nations people's perspectives on barriers and supports for enhancing HPV vaccination: foundations for sustainable, community-driven strategies. Gynecol Oncol 2018;149:93–100.
20 Garland SM, Brotherton JML, Condon JR, *et al*. Human papillomavirus prevalence among Indigenous and non-Indigenous Australian women prior to a national HPV vaccination program. BMC Med 2011;9:104.
21 O'Brien BA, Mill J, Wilson T. Cervical screening in Canadian first nation Cree women. J Transcult Nurs 2009;20:83–92.
22 Whop LJ, Garvey G, Baade P, *et al*. The first comprehensive report on Indigenous Australian women's inequalities in cervical screening: a retrospective registry cohort study in Queensland, Australia (2000–2011). Cancer 2016;122:1560–9.
23 Shannon GD, Franco OH, Powles J, *et al*. Cervical cancer in Indigenous women: the case of Australia. Maturitas 2011;70:234–45.
24 Maar M, Burchell A, Little J, *et al*. A qualitative study of provider perspectives of structural barriers to cervical cancer screening among first nations women. Women's Health Issues 2013;23:e319–25.
25 Decker KM, Demers AA, Kliewer EV, *et al*. Pap test use and cervical cancer incidence in first nations women living in Manitoba. Cancer Prev Res 2015;8:49–55.
26 Craig Rushing S, Stephens D, Shegog R, *et al*. Healthy native youth: improving access to effective, Culturally-Relevant sexual health curricula. Front Public Health 2018;6:225.
27 Balbinotto G, Jardim A. Epidemiology and economic impact of cervical cancer in the state of Romania (Brazilian Amazonic region); the perspective of the Brazilian unified health system. Int J Gynaec Obs 2012;119:S3.
28 Cervantes J, Lema C, Hurtado L, *et al*. Prevalence of human papillomavirus infection in rural villages of the Bolivian Amazon. Rev Inst Med Trop Sao Paulo 2003;45:131–5.
29 Demers A, Shearer B, Totten S, *et al*. P1-S2.69 prevalence of HPV infections in Metis and first nations living in Manitoba, Canada. Sex Transm Infect 2011;87:A152.

30 Blakely T, Kvizhinadze G, Karvonen T, *et al*. Cost-Effectiveness and equity impacts of three HPV vaccination programmes for school-aged girls in New Zealand. Vaccine 2014;32:2645–56.
31 Deluca GD, Basiletti J, Schelover E, *et al*. Chlamydia trachomatis as a probable cofactor in human papillomavirus infection in Aboriginal women from northeastern Argentina. Braz J Infect Dis 2011;15:567–72.
32 Rhodes JE. A model of youth mentoring. In: DuBois D, Karcher M, eds. Handbook of youth mentoring. Thousand Oaks, CA: Sage Publications, 2005: 30–43.
33 Goldenberg SM, Strathdee SA, Gallardo M, *et al*. "Over here, it's just drugs, women and all the madness": The HIV risk environment of clients of female sex workers in Tijuana, Mexico. Soc Sci Med 2011;72:1185–92.
34 Bronfenbrenner U. Developmental research, public policy, and the ecology of childhood. Child Dev 1974;45:1–5.
35 McLeroy KR, Bibeau D, Steckler A, *et al*. An ecological perspective on health promotion programs. Health Educ Q 1988;15:351–77.
36 Moher D, Liberati A, Tetzlaff J, *et al*. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6:e1000097.
37 Petticrew M, Roberts H. Systematic reviews in the social sciences. Oxford, UK: Blackwell Publishing, 2006.
38 The Joanna Briggs Institute. Joanna Briggs Institute Reviewers' Manual. 2014 ed. Adelaide: The Joanna Briggs Institute, 2014.
39 Tucker JD, Tso LS, Hall B, *et al*. Enhancing public health HIV interventions: a qualitative Meta-Synthesis and systematic review of studies to improve linkage to care, adherence, and retention. EBioMedicine 2017;17:163–71.
40 Allen-Leigh B, Uribe-Zúñiga P, León-Maldonado L, *et al*. Barriers to HPV self-sampling and cytology among low-income Indigenous women in rural areas of a middle-income setting: a qualitative study. BMC Cancer 2017;17:734.
41 Adcock A, Cram F, Lawton B, *et al*. Acceptability of self-taken vaginal HPV sample for cervical screening among an under-screened Indigenous population. Aust N Z J Obstet Gynaecol 2019;59:301–7.
42 Cerigo H, Macdonald ME, Franco EL, *et al*. Inuit women's attitudes and experiences towards cervical cancer and prevention strategies in Nunavik, Quebec. Int J Circumpolar Health 2012;71:17996.
43 Tratt E, Sarmiento I, Gamelin R, *et al*. Fuzzy cognitive mapping with Inuit women: what needs to change to improve cervical cancer screening in Nunavik, Northern Quebec? BMC Health Serv Res 2020;20:529.
44 Zehbe I, Wakewich P, King A-D, *et al*. Self-Administered versus provider-directed sampling in the Anishinaabek cervical cancer screening study (ACCSS): a qualitative investigation with Canadian first nations women. BMJ Open 2017;7:e017384.
45 Butler TL, Anderson K, Condon JR, *et al*. Indigenous Australian women's experiences of participation in cervical screening. PLoS One 2020;15:e0234536.
46 Vallesi S, Wood L, Dimer L, *et al*. "In Their Own Voice"—Incorporating Underlying Social Determinants into Aboriginal Health Promotion Programs. Int J Environ Res Public Health 2018;15:1514.
47 Reilly RE, Doyle J, Bretherton D, *et al*. Identifying psychosocial mediators of health amongst Indigenous Australians for the heart health project. Ethn Health 2008;13:351–73.
48 Barnett L, Kendall E. Culturally appropriate methods for enhancing the participation of Aboriginal Australians in health-promoting programs. Health Promot J Austr 2011;22:27–32.
49 Lechner M, Breeze CE, O'Mahony JF, *et al*. Early detection of HPV-associated oropharyngeal cancer. Lancet 2019;393:2123.

End of Published Paper

8.6 SUPPLEMNENTARY FILES

8.6.1 Search strategy and logic grid

Logic Grid: **PubMed: 153: 11/10/2019**

HPV AND INDIGENOUS POPULATIONS

HPV	Indigenous Populations
HPV [Text Word] OR "papillomaviridae"[MeSH Terms] OR "human papillomavirus" [MeSH] OR "human papillomavirus" [Text Word] OR "human papillomavirus 16"[MeSH Terms] OR human papillomavirus 16 [Text Word] OR "human papillomavirus 18" [MeSH Terms] OR human papillomavirus 18 [Text Word] OR papillomavirus [Text Word]	("first nation"[Text Word]) OR "first nations"[Text Word]) OR "pacific islander"[Text Word]) OR "pacific islanders"[Text Word]) OR "torres strait islander"[Text Word]) OR "torres strait islanders"[Text Word]) OR aborigin*[Text Word]) OR africa*[Text Word]) OR alaska*[Text Word]) OR aleut*[Text Word]) OR amerind*[Text Word]) OR arctic[Text Word]) OR aymara[Text Word]) OR bushmen[Text Word]) OR chukchi[Text Word]) OR chukotka*[Text Word]) OR circumpolar[Text Word]) OR eskimo*[Text Word]) OR greenland*[Text Word]) OR hmong[Text Word]) OR indian*[Text Word]) OR indigen*[Text Word]) OR inuit*[Text Word]) OR inupiaq[Text Word]) OR inupiat[Text Word]) OR khanty[Text Word]) OR maori*[Text Word]) OR mapuche[Text Word]) OR metis[Text Word]) OR native*[Text Word]) OR navaho*[Text Word]) OR navajo*[Text Word]) OR nenets[Text Word]) OR quechua[Text Word]) OR saami[Text Word]) OR sami[Text Word]) OR samoan*[Text Word]) OR siberia*[Text Word]) OR skolt[Text Word]) OR tribal[Text Word]) OR tribe*[Text Word]) OR xingu*[Text Word]) OR yup'ik[Text Word]) OR yupik[Text Word]) OR zuni[Text Word]) OR "African continental ancestry group"[Mesh]) OR "African continental ancestry group"[Mesh]) OR "Asian continental ancestry group"[Mesh]) OR "Health Services, Indigenous"[Mesh]) OR "Oceanic ancestry group"[Mesh]) OR "arctic regions"[Mesh]) OR "ethnic groups"[mesh]

Logic Grid: **EMBASE: 271 : 21/08/2020**

HPV	Indigenous Populations
('human papillomavirus type 16':ti,ab,kw OR 'human papillomavirus type 18':ti,ab,kw OR 'wart virus':ti,ab,kw OR 'oral human papillomavirus infection':ti,ab,kw OR 'hpv':ti,ab,kw)	'indigenous population':ti,ab,kw OR 'indigenous people':ti,ab,kw OR 'Samoan (people)':ti,ab,kw OR 'First Nation':ti,ab,kw OR 'Pacific Islander':ti,ab,kw OR 'Torres Strait Islander':ti,ab,kw OR 'Black person':ti,ab,kw OR 'Alaska Native':ti,ab,kw OR 'Aleut (people)':ti,ab,kw OR 'Amerind people':ti,ab,kw OR 'Aymara (people)':ti,ab,kw OR 'Chukchi (people)':ti,ab,kw OR 'Chukotka':ti,ab,kw OR 'Eskimo-Aleut people':ti,kw,ab OR 'Greenland':ti,ab,kw OR 'Hmong (people)':ti,kw,ab OR 'Indian':ti,ab,kw OR 'indigenous people':ti,kw,ab OR 'Inuit':ti,kw,ab OR 'Inupiat (people)':ti,kw,ab OR 'Khanty (people)':ti,ab,kw OR 'Maori (people)':ti,kw,ab OR 'Mapuche (people)':ti,kw,ab OR 'indigenous people':ti,kw,ab OR 'Navajo (people)':ti,kw,ab OR 'Nenets (people)':ti,kw,ab OR 'Quechua (people)':ti,kw,ab OR 'Sami (people)':ti,kw,ab OR 'Yupik (people)':ti,ab,kw OR 'Zuni (people)':ti,ab,kw OR 'Asian continental ancestry group':ti,ab,kw OR 'Oceanic ancestry group':ti,ab,kw OR 'Arctic':ti,ab,kw OR 'ethnic group':ti,kw,ab

Logic Grid **SCOPUS: 764: 21/08/2020**

HPV	Indigenous Populations
TITLE-ABS-KEY (HPV) OR TITLE-ABS-KEY (papillomaviridae) OR TITLE-ABS-KEY (human papillomavirus) OR TITLE-ABS-KEY (human papillomavirus type 16) OR TITLE-ABS-KEY (human papillomavirus type 18)	TITLE-ABS-KEY (Indigenous AND population) OR TITLE-ABS-KEY (ethnic AND groups) OR TITLE-ABS-KEY (aborigin) OR TITLE-ABS-KEY (torres AND strait AND islander) OR TITLE-ABS-KEY (black AND person)

Web of Science: 189 :21/08/2020

HPV	Indigenous Populations
(HPV OR human papillomavirus OR human papillomavirus type 16 OR human papillomavirus type 18 OR Oral HPV OR wart virus)	**TOPIC:** ((first nation OR first nations OR pacific islander OR pacific islanders OR torres strait islander OR torres strait islanders OR aborigin* OR africa* OR alaska* OR aleut* OR amerind* OR arctic OR aymara OR bushmen OR chukchi OR chukotka* OR circumpolar OR eskimo* OR greenland* OR hmong OR indian* OR indigen* OR inuit* OR inupiaq OR inupiat OR khanty OR maori* OR mapuche OR metis OR native* OR navaho* OR navajo* OR nenets OR quechua OR saami OR sami OR samoan* OR siberia* OR skolt OR tribal OR tribe* OR xingu* OR yup'ik OR yupik OR zuni OR African continental ancestry group OR African continental ancestry group OR Asian continental ancestry group OR Health Services, Indigenous OR Oceanic ancestry group OR arctic regions OR ethnic groups))

8.6.2: JBI SUMARI appraisal tool questionnaire for qualitative systematic reviews

1. Is there congruity between the stated philosophical perspective and research methodology?
2. Is there congruity between the research methodology and the research question or objectives?
3. Is there congruity between the research methodology and the methods used to collect the data?
4. Is there congruity between the research methodology and the representation and analysis of data?
5. Is there congruity between the research methodology and the interpretation of results?
6. Is there a statement placing the researcher culturally or theoretically?

7. Is the influence of the research on the researcher and vice versa, addressed?
8. Are the participants and their voices adequately represented?
9. Is there research ethical according to current criteria or, for recent studies, and there evidence for ethical approval by an appropriate body?
10. Do the conclusions drawn in the research report flow from the analysis, or interpretation of the data?

8.6.3 Appraisal of the included studies

Citation	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10
Adcock A. 2019.	Y	Y	Y	Y	Y	N	N	Y	Y	Y
Allen-Leigh B et al. 2017.	Y	Y	Y	Y	Y	N	U	Y	Y	Y
Cerigo H et al. 2012.	Y	Y	Y	Y	Y	N	N	Y	Y	Y
Cui Y et al. 2010.	Y	Y	Y	Y	Y	N	N	N	Y	Y
Henderson R et al. 2018.	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Maar N et al. 2016.	Y	Y	Y	Y	U	Y	U	Y	Y	Y
O'Brien B et al. 2009.	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Tratt E et al. 2020.	Y	Y	Y	Y	Y	Y	U	Y	Y	Y
Wakewich P et al. 2015.	Y	Y	Y	Y	Y	Y	N	Y	Y	Y
Zehbe et al. 2017.	Y	Y	Y	Y	Y	Y	N	Y	Y	Y
%	100.0	100.0	100.0	100.0	90.9	63.63	18.18	90.9	100.0	100.0

8.6.4: List of study findings with illustrations

Study: Tratt E et al 2020	
Finding	Cultural Awareness (C)
Illustration	Cultural awareness of healthcare workers was a major facilitator, reflected in positive patient experiences and more use of adequate communication means. (Pg 3)
Finding	Previous Experiences (C)
Illustration	Previous positive experiences of health personnel in their interaction with Inuit was told to be a factor that highly contributes to increase cultural awareness, countering the negative effect of a healthcare system based on non-Inuit cultural values. (Pg 4)
Finding	Increased confidence in patients' capabilities (C)
Illustration	Thus, allowing a more active role of patient in decision-making. (Pg 4)
Finding	Access to medical information (C)
Illustration	The vast majority of participating women expressed the need to get screened after understanding medical facts, including but not limited to the absence of symptoms (Pg 4)
Finding	Personal Preference (U)
Illustration	"For me, I am used to getting my Pap, I'm fine with it. But for the younger girls, [or] the shy ones, [or] those who were sexually abused, they might prefer [the HPV self-sampling method]." (Pg 4)
Finding	Means of communication (C)
Illustration	Participants reported the major importance of using visual language, ranking higher than using Inuktitut, and they stressed the communication problems behind using French or medical jargon. (Pg 4)
Study: O'Brien B et al 2009	
Finding	Vivid Recollection of healthcare encounters (U)
Illustration	"My appointment was scheduled when the offices are closed so I knew he was going to be giving me some fairly bad news. The office was empty, and the lights were all turned down. It was a real comfortable surrounding. He gave me a lot of information, pamphlets, and people to phone for support." (Pg 85)
Finding	Not Knowing what was happening (inadequate explanations) (U)

Illustration	"I still don't know, to this day, whether they found anything or what portion they removed, if they even removed anything. I don't know! Nobody explained anything to me because, maybe because I didn't ask. Maybe they thought that I understood everything that was going on, but I didn't." (Pg 86)
Finding	Not knowing what was happening (Confusion) (U)
Illustration	"When you're in (western Canadian city A) and (western Canadian city B) sometimes you just get pushed along as if you're just a file. "Here you go, this is what's wrong, this is what we're going to do, see you later." I don't understand where I go from there, how's my health going to be affected by it now." (Pg 86)
Finding	Encouragement and Support (Fear of process) (U)
Illustration	"My mom has gone through the process. She told me that she had cancer in her cervix and that she had to go for surgery. So it was a big fear for me because as soon as you hear cancer you think of the ultimate. There's nothing more then; but for this person to die. "(Pg 86) "My dad had a really difficult time with it, because he was already in his early 60s at the time, and as soon as he heard cancer [he thought] I was going to die. He started cutting off the emotional ties with me then." (Pg 86) "People are scared. I'm thinking of my sister. She hasn't gone back to get retested. She did have an abnormal result the first time. I think she's afraid. Some people are afraid that if they do find cancer, it's downhill from there." (Pg 86) "To find out that I have some kind of illness . . . like to know you're sick you just want to block it out. . . . If I knew I had an illness . . . I would probably just shut down from everything and totally change, and not for the better either." (Pg 86)
Finding	Encouragement and Support (Motivation) (U)
Illustration	"My fear is of having [cervical cancer] . . . motivates me. I want to have good health. I don't want that kind of a disease." (Pg 86)
Finding	Encouragement and Support (Support) (U)
Illustration	"I would try and keep encouraging her . . . to tell her, "If they find it early they can do something about it." I try and set examples for my clients. I tell people, "Did you know this lady had this kind of cancer because she never got tested, and they could have done something about it right away and she would still be here."" (Pg 86)
Finding	Encountering a male provider (Traditional Beliefs) (U)

Illustration	"I had it done by a male doctor and I was uncomfortable . . . because of the way I was raised. My [traditional] grandmother always told me that the only man that should know you like that is your husband." (Pg 87)
Finding	Encountering a male provider (Nervousness) (U)
Illustration	"My first Pap smear was done by a male and I was very nervous and I just didn't want it done. Maybe that's why I didn't have another one [Pap smear] . . . because of that [male gender]." (Pg 87)
Study: Maar N et al 2016	
Finding	(Explain the value of cervical screening) Importance & Benefits (U)
Illustration	"Explain [what the Pap test is] then they accept the value of early diagnosis: I find that once I explain to them the importance of early detection and [that] it can be treated, they're more agreeable to [a Pap test]." (Pg 4)
Finding	(Explain the value of cervical cancer screening) Awareness of screening services (U)
Illustration	"The biggest motivation is education, I think. You know, just teach them, let them know that the service is there, that they need to take it, it's important that they have it." (Pg 4)
Finding	(Explain the value of cervical cancer screening) Screening can prevent cancer (U)
Illustration	"We know cervical cancer is 100% preventable, and I know because I read stats and see statistics that Aboriginal women are the number one on the list for dying from this." (Pg 5)
Finding	(Motivate through specific educational strategies and capacity building) Build local HCP capacity (U)
Illustration	"You need to make sure that you train the trainers, like teach the CHRs [community health representatives], and the women in the community that are providing service." (Pg 5)
Finding	(Motivate through specific educational strategies and capacity building) Education by community cancer survivors (U)
Illustration	"I think if there was someone just sharing stories. If a woman was willing to share her story that she's had this and got screened early. Girls like to listen to things like that, and the women like to listen to things like that. I beat this and I did that. Something like that would motivate them." (Pg 5)
Finding	(Motivate through specific educational strategies and capacity building) Education by extended female relatives (U)

Illustration	"Well, my mother, you know, always went for her physicals; thus I learned that I was to go for my physicals... the families that do have it, you can see that progression of preventative health care." (Pg 5)
Finding	(Motivate through specific educational strategies and capacity building) Early education in schools (U)
Illustration	"Start early, in school already: we should get our younger girls out there, and have that part as [education], at [grade] 8, and I know they're doing great in the school, getting it out there, about STDs." (Pg 5)
Finding	(Motivate through specific educational strategies and capacity building) Regular workshops (U)
Illustration	"Workshops, information sessions: I have lunch and learns. That's a start. There's all different venues bringing that into the community." (Pg 5)
Finding	(Motivate through specific educational strategies and capacity building) Passive intervention for whole community (U)
Illustration	"You could even [do] something as simple as Facebook. Everybody's on Facebook." (Pg 5)
Finding	(Motivate through specific educational strategies and capacity building) Include humour in health education (U)
Illustration	"We didn't specifically talk about HPV, but we talked about STDs [during the education session]. Yeah, I think they got it because they still, when they see me on the streets here, we kind of giggle about it because we used bananas [for the sex education], you know, and they'll ask me: "Are you bringing bananas next week?" You know, so, it was a fun thing." (Pg 6)
Finding	(Motivate through specific educational strategies and capacity building) Use local language (U)
Illustration	"I have a sweet little old lady, she's probably close to 80; she won't speak it, she won't speak English, she understands you, she can speak English, but she would rather speak in her own language." (Pg 6)
Finding	(Embed cervical cancer screening into community events) Integrate screening into wellness events (U)
Illustration	"So if you're having something that they're able to come and access, [like a] sewing circle, or community kitchen, something that they're gonna get, then they'll come." (Pg 6)
Finding	(Embed cervical cancer screening into community events) Screening on days that honour women (U)

Illustration	"I would concentrate on a day that's important to the women, like Mother's Day. The mothers would all come and the grandmas would come and the aunts would come. I would have guest speakers come in as well and there would be a dinner, a luncheon, or a feast of some sort. I would bring somebody in who had a little bit of charisma like a Tai Chi instructor who cooks meals" (Pg 6)
Finding	(Embed cervical cancer screening into community events) Small incentives (U)
Illustration	"It's hard to get people coming unless we have food and incentives." (Pg 6)
Finding	(Health care providers need a trusting rapport with women) Friendly Relationship (U)
Illustration	"The women are, you know, fairly open once they're comfortable." (Pg 6)
Finding	(Health care providers need a trusting rapport with women) Trusting Relationship (U)
Illustration	"It's all about trust and relationships, like if you can't build a relationship you're not gonna get anywhere, you might not even see them again." (Pg 7)
Finding	Integrate cervical cancer screening recruitment into existing health care services (U)
Illustration	"Well, since you're here, you know, we haven't screened for this, and when was your last Pap and what about colon cancer screening?" (Pg 7)
Finding	(Create a dialogue on cervical cancer screening in day-to-day activities) Sustain screening culture with HCP (U)
Illustration	"For our little group of work girls, [the] service team, we always tend to remind each other as well, like, "Hey, is it time for your check-up yet, like?"" (Pg 7)
Finding	(Create a dialogue on cervical cancer screening in day-to-day activities) Word of mouth reminders (U)
Illustration	"I think it's just sort of word of mouth, spreading things around, and just kind of bringing it up, you know, all the time." (p. 7) "I call four people and then each one of the people I call, they call four people and it's something that we're trying to work on." (Pg 7)
Finding	(Incorporate First Nations gender perspective on body and preferred screening techniques to enhance privacy and comfort) Screening as a way for women to re-gain teaching roles (C)

Illustration	"The regular program for girls meets every second Monday, and it's called the Moon Time Girls." (Pg 7)
Finding	(Incorporate First Nations gender perspective on body and preferred screening techniques to enhance privacy and comfort) Holistic approach for cultural integrity (U)
Illustration	"Well, word it a way to have to do with childbearing, [which] is a sacred gift that's only given to women, let's keep our bodies healthy by getting annual check-ups, and you use some culturally appropriate like pictures, or something." (Pg 8)
Finding	(Incorporate First Nations gender perspective on body and preferred screening techniques to enhance privacy and comfort) Using non-invasive screening (U)
Illustration	"Informant #14: I think that's the best idea that has come out of anything, like it's not invasive, you do it in your own home, at your own time... I.Z.: Whenever you, you know, are ready for it and... Informant #14: I think that with education along with it that this is what it is, I think that the success rate will be phenomenal with it because it's in their own home." (Pg 8)
Finding	(Incorporate First Nations gender perspective on body and preferred screening techniques to enhance privacy and comfort) Multi-purpose screening (U)
Illustration	"If it [other STI testing] can be done on the same swab [as self-sampling], I would say, the value of that would be huge." (Pg 8)
Finding	(Incorporate First Nations gender perspective on body and preferred screening techniques to enhance privacy and comfort) Preference of female HCP (U)
Illustration	"The girls are always looking for female doctors" (Pg 8)
Study: Allen-Leigh B et al 2017	
Finding	Beliefs and knowledge about cervical cancer (Correct knowledge) (U)
Illustration	"If you detect it in time, you can take that sickness out so it won't progress any more and with a treatment you are fine." (Pg 4)
Finding	Beliefs and knowledge about cervical cancer (Incorrect knowledge) (U)
Illustration	"Between these two sicknesses [HPV and cervical cancer] we're in danger, we should go to the clinic or a doctor. If we feel pain in the womb, go to a doctor." (Pg 4)
Finding	Perceptions of and knowledge about HPV (Correct knowledge) (U)

Illustration	[Cervical cancer is caused] "by infections, because later they become like a tumor in the womb." (Pg 4) "There is a vaccine for human papillomavirus. I heard it on the radio, that there are vaccines." (Pg 4)
Finding	Perceptions of and knowledge about HPV (Combined correct and incorrect knowledge) (U)
Illustration	"Well, as far as I know, the virus is transmitted through sexual contact. Then this human papillomavirus, it begins without any warning. Then later it progresses, then the discomfort in our parts [genitals] begins and that's when the discharge starts and it progresses to the cervix and when it gets to the cervix it goes into the uterus and that is when the doctor sends us for an operation." (Pg 4)
Finding	Perceptions, knowledge and experiences related to cytology (Combined correct and incorrect knowledge) (U)
Illustration	"Moderator: What is cervical cancer, what do you know about cervical cancer? Huichol woman 1: They say you can die of cancer, if you don't detect it early. Moderator: And how do you detect it? Huichol woman 1: With the Papanicolaou, doing it periodically. Moderator: And what's periodically? Huichol woman 1: Every three months. Moderator: Everyone, how often do you think you need to get a Papanicolaou? Huichol woman 2: Once a year. Huichol woman 3: Depends on how you feel, once a year or every two years, I get it every two years. Moderator: What do you mean, how you feel? Huichol woman 3: If you feel burning." (Pg 4)
Finding	Barriers to cervical cancer screening using cytology or the HPV self-sampled test (Pain and fear of unsterile equipment as a barrier) (U)
Illustration	"[When they did the Papanicolaou test], maybe they did it wrong. I don't know, but I felt something like a scrape. Then I thought maybe the equipment wasn't disinfected. ... I thought about it a lot before doing it again, because I was afraid." (Pg 4)
Finding	Barriers to cervical cancer screening using cytology or the HPV self-sampled test (Not receiving test results as a barrier) (U)
Illustration	"A lot of us say, and we've talked about this before, when we get a Papanicolaou, the results don't arrive, and we don't know what it is that's going on. There we are with the doctor, asking why the results don't arrive. ... Whatever it [the result] is, they should give it to me." (Pg 4)
Finding	Barriers to cervical cancer screening using cytology or the HPV self-sampled test (Unequal gender relations as a barrier) (U)

Illustration	"The first time I went to check myself, with the Papanicolaou tests, I had problems. I got beat-up. My husband hit me because he said I had gone to do things with the [male] doctor. When it wasn't even a doctor who examined me, the [female] nurse examined me! She took the sample, but at home my husband didn't believe that." (Pg 4)
Finding	Barriers to cervical cancer screening using cytology or the HPV self-sampled test (Lack of gender-related barriers) (U)
Illustration	"Because with all these [health education] talks they give us, women are more secure in themselves. So, we don't really ask men for permission anymore, because it's something that's good for us." (Pg 4) "I decided it [to perform the HPV test] myself, alone. I don't ask anyone's permission. ... How am I going to ask him if he [her husband] wants it or not? It's not for him, it's for me." (Pg 4)
Finding	Perceived advantages of the self-sampled HPV test (Less embarrassment) (U)
Illustration	"This one [the HPV test] is good because it [cytology or the Papanicolaou test] really does embarrass you, not because your husband doesn't want it or doesn't let us, but because it's embarrassing and because of embarrassment we don't do it, and so this [self-sampled HPV test] is good for us." (Pg 5) "Because you do it yourself, since always, even if there is trust, you feel a little embarrassed to undress in front of someone else" (Pg 5)
Finding	Perceived advantages of the self-sampled HPV test (More comfortable) (U)
Illustration	"Well, this one [the self-sampled HPV test] is better, because it is more comfortable to do it." (Pg 5)
Study: Cerigo H et al 2012	
Finding	Experiences, Attitudes and beliefs about cervical cancer (C)
Illustration	A sizable proportion of the women were unable to identify a cervical cancer risk factor and were unsure if detecting cervical cancer early would affect the chance for a cure. (Pg 5)
Finding	Pap smear history, understanding and experiences (female preference) (U)
Illustration	""Some people don't go [to get Pap smears], maybe they're shy … all of my friends don't go probably because they are shy or sometimes they don't want to [be] checked by a man, if it is a man that is a nurse." (Pg 3)

Finding	Pap smear history, understanding and experiences (embarrassment) (C)
Illustration	Feelings of embarrassment and pain during Pap smears were common among our study population and others. Among our population, older women reported more feelings of embarrassment than the young women. (Pg 5)
Finding	Pap smear history, understanding and experiences (lack of knowledge) (C)
Illustration	Further, we found that some women did not fully understand the purpose of the Pap smear as a method of cervical cancer screening, as 30% reported that the purpose of the Pap smear test is to screen for STIs. (Pg 5)
Study: Zehbe et al 2017	
Finding	Educational implications (contribution to stereotype) (U)
Illustration	Focus group participants were concerned that any publication of information about HPV rates on reserve could have negative effects, contributing to the stereotype that 'all native people have HPV' (FG6). As one HCP summarised: 'A lot more education has to be done about HPV and cervical cancer together' to alleviate these concerns (Pg 7)
Finding	Educational implications (women blamed for STI's) (U)
Illustration	"'HPV, like, whoa, I don't have that, like, I don't even want to know if I have that" (Pg 7) 'because it's a relationship thing' that implied that someone had 'cheated' (Pg 7) '…. do they [the men] not need to know some of this stuff too?' (Pg 7) '… I know only women get cervical cancer but … they've helping it along in the same sense where they've passing it back and forth' (Pg 7)
Finding	Educational implications (need to explain self-sampling) (U)
Illustration	HCPs felt that education around self-testing might better be done in the context of a well woman healthcare visit, as 'part of a physical, that might get best [results]' (Pg 7) Women would not necessarily understand that they would still need to go to their HCP for other reproductive healthcare: 'They would, they'd probably think, well, I've had that done, so I don't need this done'" (Pg 7) "If you hand me a kit, I won't touch it. Because I wouldn't know what to do, what if I did it wrong, or whatever, right, so? And I think a lot of

	people would be that way" (pg 7) 'you just give a test kit to them at home; the majority of them are just going to throw them out.'(Pg 7)
Finding	Convenience factor self-sampling (no appointment needed) (U)
Illustration	'It is more comfortable to do it at home … it's simple'. (Pg 6) I think the self-test is beneficial for them all because sometimes people don't have time for appointments to take off work, it [the Pap] is kind of an inconvenience' (Pg 6) 'would go for it' (Pg 6) older woman who had fewer constraints 'were used to getting Paps' (Pg 6) "Even hearing [about self-testing], people are just, What? Oh, I'd do that, for sure, instead of me going to the doctor' " (Pg 6) "Doing a self-test doesn't take very long … it's something that can be dealt with, done, gone' (Pg 6) " I really strongly believe that … because I was the one that was doing it [self-sampling], I was the one that was in control … and this way it gave me the ability to do it myself and I got all the results, they were fine; … it was also self-empowering, great, I like that." (Pg 6)
Finding	Convenience factor self-sampling (more privacy) (U)
Illustration	"I think more people would monitor it that way and test it themselves, like 'well maybe not today, but … eventually I'm going to try it' (Pg 6) option of taking it home might make women 'feel more empowered' and contribute to a better relationship with HCPs. (Pg 6) An option, they can either do it themselves, or you can offer to do it for them' (Pg 6)
Finding	Psychological comfort (high comfort with self-sampling) (U)
Illustration	"doing it yourself would be better" "would feel more comfortable with that [self-test] than a male doctor" (Pg 6) 'shy' of doctors or nurses who visited the communities. (Pg 6) Self-testing would also address the 'trust issues' that discouraged women from seeking care from non-indigenous HCPs. (Pg 6)
Finding	Psychological comfort (male providers) (U)
Illustration	"feel more comfortable [with a female physician or nurse practitioner] because maybe she's going through the same thing that you're going through." (Pg 6)

	"embarrassed anyway, no matter who did it (Pg 6) "I only got a Pap test once and I got it from a woman … and she was trying to make me feel comfortable, but it's still really awkward" (Pg 6)
Finding	Physical comfort level (self-sampling is less painful) (U)
Illustration	"Women wouldn't be so agitated and nervous about having the [self-] test'"(Pg 5) "It's a lot less clinical … stripping down and allowing someone else to do the scraping of the cervix, the whole uncomfortable procedure of going through a Pap opposed to doing it privately in the bathroom on your own is a huge difference.' '…I think the prevalence [participation] rate would go up' (Pg 5) "It's a lot less clinical … stripping down and allowing someone else to do the scraping of the cervix, the whole uncomfortable procedure of going through a Pap opposed to doing it privately in the bathroom on your own is a huge difference.' '…I think the prevalence [participation] rate would go up'" (Pg 5)
Finding	Physical comfort level (paps hurt) (U)
Illustration	"it's kind of a routine after a while … they open you up and they swab and then you're done" (Pg 5) "the Pap is uncomfortable but it has to be done" (Pg 5) "it doesn't get any easier, like the first time and then the next year, it didn't get any easier for me" (Pg 5) "I didn't like the way it felt, that's why I didn't want to go back there' They don't want their Paps [be]cause it hurt." (Pg 5) The test also could be exceptionally painful if providers were 'in a rush' or 'rough' and did the procedure 'real quick' (Pg 5) "Some women, when they come to the appointment, they decide they don't want to get a Pap, because it's uncomfortable, they're just afraid" (Pg 5)
Finding	Cervical Screening practices in partner communities (privacy concerns) (U)
Illustration	"health centres where staff 'phoning people, telling them, 'we've got your results … you need to make another appointment' (FG2) was upsetting." (Pg 5) "I don't want nobody else to know' 'a lot more private, at home, if you do it by yourself'(Pg 5)

	"Women would prefer to be discreet, do it themselves and get their own results and not have their results shared with others" (Pg 5)
Finding	Cervical Screening practices in partner communities (no efficient follow up) (U)
Illustration	"It's crazy here, how long you have to wait for anything and half the time, you don't even get a call … you go to your next doctor's appointment for something else and [have to ask] … by the way, how about my Pap two months ago?" (Pg 5)
Finding	Cervical Screening practices in partner communities (transportation and child care issues) (U)
Illustration	"If the van was full, [you would] have to get a ride … some of us don't have cars, you know" (Pg 5) Women with children and work commitments also had difficulty arranging childcare and time off work to keep their appointments. As a HCP commented: 'It certainly does pose challenges with regards to babysitting care and the mother being away for an entire day' (Pg 5)
Finding	Cervical Screening practices in partner communities (lack of provider flexibility) (U)
Illustration	"I don't know how many times they've cancelled Pap tests and [when I asked] "okay well can I get it on Friday? …. [heard back] "No, we don't do them on Friday"" (Pg 5)
Finding	Cervical Screening practices in partner communities (no regular screening service) (U)
Illustration	""Most of us do not have doctors here … you have to drive up to [nearby town]"" (Pg 4)
Study: Adcock A 2019	
Finding	Engagement with health services (C)
Illustration	One in seven (14.36%) had not screened in ten years or more (including those never screened), and one in six (16.37%) were unsure how long it had been since their last cervical screen. (Pg 2)
Finding	Barriers to screening (shyness, embarrassment) (C)
Illustration	Desire for bodily autonomy (retaining privacy, control over one's body) as a reason for not attending regular cervical screening. (Pg 3) encompasses concepts of whakamā (embarrassment/shyness/reticence), (Pg 3) tapu (sacred/taboo/forbidden) (Pg 3)

	desire for bodily autonomy was often related to negative health experiences (eg, painful pelvic examinations, inappropriate actions/comments by HCPs) (Pg 3)
Finding	Barriers to screening (cost) (C)
Illustration	Older women were more likely to mention a previous bad experience and were less likely than younger women to mention cost or other financial barriers (Pg 3) Opinions varied about cost being a barrier (as many clinics offer free cervical screening). (Pg 3) Some highlighted hidden costs (transport, parking, childcare) (Pg 3)
Finding	Barriers to screening (education) (C)
Illustration	A lack of health literacy about HPV and cervical cancer and a lack of appropriate/empathetic services were also raised as barriers. (Pg 3) relationship-building between communities and health promoters; including whānau/family in HPV education; and ensuring clear information about HPV vaccination (Pg 3) HCPs agreed that with appropriate support and education, HPV self-testing will benefit never/under-screened Māori. (Pg 4)
Finding	Acceptability (U)
Illustration	positive, with participants using terms such as 'easier', 'more comfortable', 'less intrusive' and 'brilliant'. (Pg 3) Nearly two-thirds (61.21%) said they would prefer an HPV self-test to a clinician-collected vaginal swab or a cervical sample collected with a speculum, or to other options. (Pg 4)
Finding	Implementation (C)
Illustration	picking up the HPV self-test from a clinic, a pharmacy or other community venue, or receiving it by post/mail (Pg 4) concerns were raised about the reliability of post. Participants discussed the value of providing multiple options (Pg 4) Flexibility to cater to diverse populations, such as through community outreach services, was suggested for optimum engagement. (Pg 5)
Finding	Doing the self-test? (U)
Illustration	most frequently said they would be happy to do the HPV self-test in a clinic or their own home, and emphasised having good support and education to increase their confidence about properly doing it. (Pg 5) need for a flexible program, with different options. (Pg 5)

	Urban women were more likely (than rural) to say they would self-test at a community centre. (Pg 5) One in five said they would like whānau/family or friends to be around in case they needed help, while some (<15%) said they would like either a community health worker or health practitioner to be nearby, available to help. (Pg 5) importance of delivering empathetic cervical screening services, ie 'the process' – taking the time to put mind and body at ease. They emphasised that this process will be important for any new HPV-based cervical screening program. (Pg 5)
Finding	HPV self-test results (C)
Illustration	if negative a text is fine, but if positive it is better to find out in person or by phone. (Pg 5) One women emphasised the importance of results being delivered in an empathetic way.(Pg 5) Older women were less likely than younger women to want to receive a text asking them to call their health practitioner.(Pg 5) Non-PHO-enrolled/unsure women were less likely to choose to receive results by email and more likely to choose a visit with a health practitioner need for clear communication (Pg 5) appropriate/empathetic support for women. (Pg 5) Concerns were raised about who would be responsible for HPV self-test results and making sure that women are added to the screening register when doing a self-test.(Pg 5)
Finding	Positive test results (C)
Illustration	mostly positive response to the idea of seeking further screening (cytology) or diagnosis (colposcopy) if a HPV test was positive – because knowing that something needs follow up would be a good motivator.(Pg 5) HCPs wanted assurance that women would be supported appropriately and empathetically to have cytology or colposcopy if they had a positive HPV self-test result, and many supported going straight to colposcopy.(Pg 5) Eliminating multiple clinic visits was stressed. (g 5)
Study: Henderson R et al 2018	
Finding	(Cancer & HPV Experiences) Disease Progression (U)
Illustration	"Once they corrected the cervical cancer you would end up with cancer somewhere else" (Pg 96)

Finding	(Cancer & HPV Experiences) Isolating Effects (U)
Illustration	"It took time for one family to realize that it was 'not just happening to them, it's the whole community'" (Pg 96)
Finding	(Cancer & HPV Experiences) Mistrust of external influences (U)
Illustration	"It must be the pesticides that are being sprayed on our cultivated land...You can see our area and there is a layer of dust in spring and harvest" (Pg 96)
Finding	(Cancer & HPV Experiences) Residential school disruption of community relationships (U)
Illustration	"Opened a whole can of worms; when all the illness and substance abuse went on a skyrocket" (Pg 96) "Speaking of a sister in the end-stage of cervical cancer, one middle-aged participant attributed the illness to chronic sexual abuse: "There were a couple times she had STIs [sexually transmitted infections] and didn't really know, may have been HPV or may have been another" (Pg 96) "In both sharing circles, participants argued that residential school litigation broke students' capacity for intimacy throughout their lives, playing out in self-destructive coping strategies (e.g., substance dependence, early sexualisation) and increased risk of victimization)" (Pg 96)
Finding	(Trauma-informed lens) Contributions of higher Indigenous HPV burden (U)
Illustration	"Our people are starving for affection, support, respect and love." (Pg 96)
Finding	(Trauma-informed lens) Residential schools (U)
Illustration	"The nuns make sure to remind you no matter what you do, you're going to hell" (Pg 96) "We were taught to be quiet about our private parts...a lot of sexual abuse went on, and spiritual, physical, you name it" (Pg 96) "One speaker brought these lingering effects of residential schools together by describing a shift in her society from monogamous relation- ships to relaxed sexual boundaries, noting that with her own daughters she "didn't lay down the law like our parents did" (Pg 96)
Finding	(Trauma-informed lens) Normalization of substance abuse among youth (U)
Illustration	"She got an STI because she was taken advantage of" (SC2) by someone other than her partner. The mother connected her daughter's

	exposure to loss of identity and heavy drinking at parties in her community. Lowered inhibitions brought on by alcohol, and illicit drug use were seen by several other speakers to have become normalized among younger generations, who "see the suffering of their parents and grandparents, and they are running to the substance abuse" (Pg 96) "In both circles, speakers expressed compassion for younger generations today: "It was a lot easier in my time because we would go to ceremonies...but today, our grandchildren are exposed to drugs, alcohol, everything" (Pg 96)
Finding	(Trauma-informed lens) Isolation (U)
Illustration	He observed that such statistics reflect disrupted connections between partners, between Elders and youth, as well as with nature and spirituality: "We are not islands, we need to be connected to people and that is what is missing" (Pg 96) "Therefore, the burden of HPV in FN people is rooted, at least in part, in efforts by people across the lifespan to cope with the violent disruption of family and community connectedness, as well as connection to land and spirituality. This burden is manifested not only in risk-taking behaviour, but also in avoidance of wider health systems: "I think First Nations don't get checked when they are supposed to, to be honest. They just wait until it is too late to help them" (Pg 97) Coming from a communal society, another participant observed that today many struggle "to fit into an individualistic society, and we don't fit" (Pg 98)
Finding	(Trauma-Informed lens) Child welfare (U)
Illustration	"A lot of those kids when they come back to the reserve they are very angry, there are a lot of things that happened [to them] that we don't know about" (Pg 97) "It's sad to say that lots of babies have been taken because their mothers were on opium, and the mothers are in treatment and are so sorry" (Pg 97)
Finding	(Family & Community) Communication (U)
Illustration	"I am learning a lot in these workshops. My mother died of stomach cancer, my sister of stomach cancer. I had 5 girls, and 4 of them went through breast cancer. My oldest daughter, her cancer spread. When they were younger, I made sure they all got their needles. But, you know, I have never had a workshop like this. If I get a cold, I can fight it off. When I got those needles, I was told I was able to fight the sicknesses; it won't kill you—that is what I was told. This is really good for my grandchildren; I will take this message home to my

	family. I have two nurses in my family, they probably know about it, but this is a really good thing I am still learning...[*speaking in Cree] *I was worried the white people would not take care of us, but they have so far [group laughs]. We need to talk to young ladies about how to take care of themselves." (Pg 97)
Finding	(Family & Community) Family (U)
Illustration	Many of the Elders emphasized that health education within Indigenous contexts is anchored in the love and care for children. For one speaker, this affection involves "hugging your children and telling them 'I love you', you don't say goodbye to anyone" (Pg 98) "If I'm drinking and drugging, then I'm going to feel guilty about taking my children to the clinic to help them live a healthier life" (Pg 98)
Finding	(Family & Community) Role of elders (U)
Illustration	"[My husband] goes and sits with the men and teaches them; for me, I can go out and explain things to the mothers and the children, and out of respect...he's getting that message across [in his sweat lodge ceremonies with men]" (Pg 98)
Finding	(Family & Community) Mistrust in HCP (U)
Illustration	"We need to talk to our people in a way they understand, no disrespect to any organization, but people don't look at that material [brochures], it's obvious that the way we deliver that message has to be different" (Pg 98) "The health centre sent out a notification and a consent form, and they listed the benefits and risks...and I paid more attention to the risks, and I decided not to allow her to be vaccinated, because as a parent I needed to do what was best for my children" (Pg 98)
Finding	(Family & Community) Youth (U)
Illustration	"There are anti-bullying programs...and there are cultural programs; some kids are brave and some are afraid of getting immunized, but all the children support each other" (Pg 98)
Finding	(Family & community) Parents & grandparents (U)
Illustration	"The best teachers are your parents" (Pg 98)
Finding	(Changing information landscapes) Lack of knowledge (U)
Illustration	"We never see a doctor. The health department has to get a hold of us, the ones that are never home. There are a lot of us in the community... We hear suddenly of these workshops and information centres in the community. We wanted to go but we had other commitments so

	needed others to go. My niece, she died about 3 years ago because she had cancer. They brought her to Edmonton, they started her on chemo...left her kids at home." (Pg 97) "One of the girls I used to visit got cervical cancer. She is very angry; she will not talk to me even though I give her support. She was told 3 years ago that she should get the tests and she didn't because she had problems for a long time." (Pg 97) One health director who was herself FN had not approved the HPV vaccine for her own daughter, believing at the time that vaccines are perhaps "not natural, that they are more chemicals given by the government to hurt us" (Pg 98)
Finding	(Changing information landscapes) new knowledge (U)
Illustration	"These young people are lucky to get these different resources...its scary when you think about it, you didn't think about [the health risk] before, because you didn't know anything about it" (Pg 98)
Study: Wakewich P et al 2015	
Finding	Negative body perceptions (stigma of sexually transmitted infections) (U)
Illustration	"Definitely there's always going to be a stigma about any kind of thing that's an STD [STI], because people think it's dirty or whatever. Like I've had people come in, like, even the girl I just saw with genital warts and she just couldn't believe it, and couldn't like fathom who she would have got it from because everyone she's been with has only been with her. Right? " (Pg 373) "Actually in the last 6 months that I've been there, I've had uh, a minimum of 5 people who have come to me who um, have been concerned about contracting STIs and did not want me writing it into their chart for fear that it would leak into the community … they're afraid of the stigma surrounding that so and a lot of times too I wasn't able to do any [cervical] screening." (Pg 373) "Health centres on reserves, don't want to spread it out too much how many people have HPV. I know how the stereotype works if we pass on the information in non-native communities they will say all native people have HPV." (Pg 373)
Finding	Negative body perceptions (body shyness) (U)
Illustration	"I remember feeling so vulnerable, just so extremely vulnerable and, and I remember at one point he [the male physician] was talking on his phone while I was up in the stirrups and I thought uh, you know, I wonder how many other patients feel like this …. There's got to be a better, kinder, gentler, more humane way to do it." (Pg 373)

Finding	Negative body perceptions (sexual abuse) (U)
Illustration	"They have been sexually abused, too, and I know like, in the past residential schools, that kind of thing, those people are just not comfortable because of their experiences in the past …. I will be here for a long time and whenever you need to see me, to come see me, so that even just that little thing and then when they do come I do see them, hopefully that trust builds up and I think that's a big piece with the First Nations." (Pg 374) "I think one of the biggest issues um, [short pause] the barriers that prevents people from going to and maybe it's cause it's taboo is because they've been sexually abused." (Pg 374)
Finding	Negative experience with governmental health service (distrust of health authorities) (U)
Illustration	"She [HCP] thinks it's her [that they don't like], 'like, why is no one coming [for screening]'… 'it's not you, it took me 20 years to get to where I'm at now, and I still get people that don't trust me.'" (Pg 374) "I guess they were told about some kind of vaccine or something, like years ago, and it was something just, to try to get rid of the Native people." (Pg 374) "My doctor who I had since my oldest was born, she just up and quit, so when my next appointment, I had this guy looking at me, it's like [pause] right, so it's not like they stick around here." (Pg 375)
Finding	Negative experience with government health service (lack of confidentiality and privacy) (U)
Illustration	"You know what, just sitting in the waiting room, the receptionists are phoning people telling them, we've got your results, you need an, you know, make another appointment, they say the name right out loud, they say what the test is." (Pg 375) "Privacy, a small town, I mean, you can hear through the walls, you know, walls talk because there's, it's all in one building and coming in here and everybody sees the first person coming in here, they come to see me, they come to see welfare, they come to see housing, they're going and everybody knows everything."(Pg 375) "Being in reserves, a lot of people know people's business and a lot of people get worried about that when you're trying to keep something personal. I mean the teddy bears talk, the leaves talk, the hydro lines talk." (Pg 375)
Finding	Role of family (mother - daughter relations) (U)
Illustration	I just taught them that sex isn't, it's not what you call dirty, you know, but there's a certain way you got to go about having, like for sex with

	a partner, you know, you got to explain that part to them, but to talk openly about sex, it's not what you call a dirty subject, yeah. If you want to know something just feel free to ask." (Pg 376) "Like my mother, you know, was the kind of woman that … when I first got my period, I didn't know what it was because that was something you don't talk about, your body like that. It's you know that's your own personal, private, so when it happened, I had absolutely no knowledge what was going on in my body … And with my daughter, I didn't want her to have that feeling, so I mean, of course I changed and I explained everything but, and then that's the way things are now, women are more informed than they have been in the past." (Pg 376)
Finding	Self-collected sampling as a way of increasing women's control of cervical screening (U)
Illustration	"think it [self-sampling] would be, I think it would be great, because it provides them with some autonomy and allows them to take control of the situation. That would be really great actually …. I think it would increase [education opportunities] actually, yup, because it's a lot less clinical right, cause like you say, it's a lot less you know, stripping down and you know, allowing someone else to do the scraping of the cervix, you know, the whole uncomfortable procedure of going through a Pap opposed to doing it privately in the bathroom on your own is a huge difference." (Pg 376) "I think it would definitely be more private … They wouldn't be so embarrassed … all kinds of people are easily embarrassed." (Pg 376) "It's simple, it's not like you are having forceps in you." (Pg 376)

09

Psycho-oncological considerations for Indigenous populations

9.1 PREFACE AND LINK TO PROJECT

The study (Study 6) presented in this Chapter is the second of two studies included in this section that address the second objective of this thesis.

As a part of the initial stages of the HPV-OPC project, there was interest from partnering Aboriginal communities about cancer and an element of fear and confusion was sensed by the Senior Indigenous Research Officer. After consultations with the study's Indigenous Reference group, questions regarding cancer in the family or community were included in the baseline questionnaire (Appendix A). The addition of this element was an attempt to understand the psycho-oncological perspectives amongst Indigenous populations. This commentary was written to reflect on the emotions a community goes through after hearing a terminal diagnosis. Recording these perspectives deemed important in the context of this study as we refer to cancer throughout questionnaires and critical reflexivity was vital.

This study utilises data collected as a part of this question and assesses the emotional responses of the participants after hearing about cancer in the family or community.

9.2 PUBLICATION DETAILS

This paper is an Invited commentary from the Journal of Cancer biology and is accepted as: Sethi S, Ju X, Hedges J, Jamieson L. Psycho-oncological considerations for Indigenous populations. Journal of Cancer Biology 2021 *(INVITED COMMENTARY*)

9.3 HIGHLIGHTS

- This paper explores emotional responses and provides an insight to understanding the perception of the impact of cancer for Indigenous Australian communities
- Cultural respect is a key factor which helps to achieve active engagement and interest by Indigenous families during the cancer journey.
- This paper provides helpful insights to improving understanding of support and care for cancer patients from Indigenous families/communities.

9.4 STATEMENT OF AUTHORSHIP

Statement of Authorship

Title of Paper	PYSCHO-ONCOLOGICAL CONSIDERATIONS FOR INDIGENOUS POPULATIONS
Publication Status	☐ Published ☑ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and Unsubmitted work written in manuscript style
Publication Details	Sethi S, Ju X, Hedges J, Jamieson L. Psychological considerations for Indigenous Populations. Journal of Cancer Biology, 2021 (Oct)

Principal Author

Name of Principal Author (Candidate)	Sneha Sethi		
Contribution to the Paper	Conceiving of Research Question Data Analysis Manuscript writing Editing and Revisions Paper submission for publication Correspondence with Editors in the publication process		
Overall percentage (%)	75%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	20/08/2021

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Xiangqun Ju		
Contribution to the Paper	Orientation on formulation of Research question Revision of Methodology Input in theory application Input in interpretation of results Revision of Manuscript		
Signature		Date	20/08/2021

Name of Co-Author	Joanne Hedges		
Contribution to the Paper	Revision of Methodology Input in theory application Input in interpretation of results Revision of Manuscript		
Signature		Date	20/08/2021

Name of Co-Author	Lisa Jamieson		
Contribution to the Paper	Orientation on formulation of Research question Revision of Methodology Input in theory application Input in Interpretation of Results Revison of Manuscript		
Signature		Date	20/08/2021

9.5 PUBLICATION

TITLE: PYSCHO-ONCOLOGICAL CONSIDERATIONS FOR INDIGENOUS POPULATIONS

Author Affiliations

Sneha Sethi[1], Xiangqun Ju[1], Joanne Hedges[1], Lisa Jamieson[1]

1. Australian Research Centre for Population Oral Health, Adelaide Dental School, Faculty of Health and Medical Sciences, University of Adelaide, Adelaide, Australia

*Corresponding Author

Sneha Sethi
PhD Student
Adelaide Dental School
University of Adelaide
Adelaide
Australia
Email: sneha.sethi@adelaide.edu.au
Ph no: +61-426169283

Introduction

Emotions significantly effect psychological well-being and have a substantial impact on health (1). The dynamic nature of the relationship between these factors is articulated by the World Health Organization: “Normally, emotions such as anxiety, anger, pain or joy interact to motivate a person to a goal-directed action. However, when certain emotions predominate and persist beyond their usefulness in motivating people for their goal-directed behaviour, they become morbid or pathological” (2). Thus, it is crucial to consider the emotional state of cancer patients and carers and routinely monitor emotional wellbeing, similar to indicators of physical health such as blood pressure, pulse rate, and temperature (1). The diagnosis of cancer is particularly difficult to navigate for carers, as treatment and support is typically limited to the cancer patient. Lack of available or adequate support can result in emotionally distressing circumstances for both families and communities.

Indigenous communities around the world have exhibited immense strength and resilience in the face of devastating impacts of colonisation, assimilation and attempted elimination of their cultures and peoples (3). Despite this fortitude, the effect of colonisation and various government policies has resulted in irreversible damage to Indigenous ways of knowing, being, and doing. The continuing influence of systemic racial discrimination and global capitalism is further attributing to the health inequities faced by Indigenous peoples (4)(5). While there has been an observed reduction in chronic disease mortality rates among Indigenous populations, rates of cancer and associated mortality have intensified (6-9). Cancer is the second most common cause of death among Indigenous peoples in Australia, and cancer survival rates are significantly lower among Indigenous compared to non-Indigenous Australians (10). The increased global burden of cancer among Indigenous populations has led to an amplified research interest (9, 11).

Connection to country is a vital spiritual connection for Indigenous peoples as it defines ancestral relationships and contributes towards culture and sovereignty (12). The connection to land and Country is continued by keeping and passing of knowledge and responsibilities. Identity, kinship, culture, health, wellness and family are also deeply embedded in this connection (13-15). Recognising these is a key pillar of the Well-being framework for Aboriginal people with chronic illness (16) and Optimal Care Pathways for Aboriginal and Torres Strait Islander people with cancer in Australia (17). The support of family and community play an indispensable role in alleviating cancer outcomes and survivorship, which can be achieved by acknowledging and respecting the family structures and values of Indigenous cultures. Most health care systems fail to recognise and acknowledge this connection in addition to the significant role of family and community (18-20). It has been reported that cultural respect is a key factor which helps to achieve active engagement and interest by Indigenous patients (21-23). For Indigenous peoples the experience of care is more elaborate as the health of an individual is determined by the emotional, cultural, social and physical well-being of an entire community (24). This is mirrored in Australia's National Aboriginal and Torres Strait Islander Cancer Framework, which specifies that optimal cancer care should be "person centred so that the whole person (including family and cultural role) is considered, and the psychosocial, cultural and supportive care needs and preferences of Indigenous people are addressed across the continuum of care" (25). Indigenous communities have suggested that individual life circumstances and personal experiences are relevant (26). Acceptance by healthcare workers about broader cultural issues and the avoidance of generalisation of all Indigenous patients could play a pivotal role in increasing engagement of families in the cancer process (26). A study from New Zealand (27) describes the cultural expectations and sensitivity anticipated from healthcare workers by Maori (Indigenous population of New Zealand) cancer patients, where the importance of having tikanga (customs

and values) processes at the hospitals is emphasized. A Maori participant in the study elaborates:

"*. . . the whole tikanga within the process. Knowing that we come with many whānau members, children, aunties, uncles, everybody wants to come, so shared rooms don't really meet our needs. Having somewhere for our children, so that they're not being a distraction or a hōhā* [nuisance], *but that they need to be there and their koro's* [grandfathers], *their nans, they need them there. ... This is part of your healing process, this is what is going to make it better for you. 'Cause in here it's a positive outlook for them and that will improve their treatment response (27)."*

It has been reported that family plays a critical role during treatment and impacts survivorship; additionally patient and health of other family members take priority over the caregiver's own health (24, 28). Risetevski and colleagues found that families often felt they did not receive supportive care and did not feel welcome in hospitals (28). The National Aboriginal and Torres Strait Islander Cancer Framework (24) emphasizes the need for families and carers to be "involved, informed, supported and enabled throughout the cancer experience" (24).

Cancer requires long term support and intervention strategies, the burden of which usually falls on informal caregivers (family). Research among cancer survivors has revealed that health behaviours and coping are interrelated, with significant implications for positive behaviour alterations and improved health (29, 30). It has been previously discussed that poor health behaviours for example stress and anxiety of informal caregivers impact the health of survivors (31-34). The fear and confusion associated with cancer demonstrates the necessity of exploring the emotional responses of Indigenous peoples on hearing Cancer in the community to improve understanding and increase support. This paper explores these emotional responses and

provides an insight to understanding the perception of the impact of cancer for Indigenous Communities

Findings from HPV-OPC study

Methodology: The data used to explore the impact of cancer diagnoses for Indigenous communities is from the HPV-OPC Human Papillomavirus and Oropharyngeal Carcinoma (HPV-OPC) project which is a prospective longitudinal cohort study based in South Australia (35). Participant eligibility was self-identification of Aboriginal and/or Torres Strait Islander status, aged 18+ years and a South Australian resident. Aboriginal Community Controlled Health Organisations (ACCHOs) were key stakeholders and heavily involved in participant recruitment at baseline. An Indigenous Reference Group was established to ensure Indigenous governance of all aspects of the project. The reference group was chaired by an Indigenous health manager and included Indigenous community members, health workers and councillors.

Baseline data was collected from February 2018 to January 2019 with 12-month follow-up data collected from February 2019 to January 2020. Information on socio-demographic factors, sexual behaviours and health-related behaviours were ascertained by self-report questionnaire, with assistance provided by the study's Senior Indigenous Research Officer (JH) where required. All components of data collection were pilot tested and tailored for cultural sensitivity.

Ethical approval was received from the University of Adelaide Human Research Ethics Committee and the Aboriginal Health Council of South Australia's Human Research Ethics Committee. All participants provided written informed consent.

Sociodemographic characteristics: Age (dichotomised based on median split at 37 years; 37 and less or 38 and more), sex (male or female), geographic location (metropolitan, i.e. residing in Adelaide, South Australia's capital city and non-metropolitan; i.e. residing elsewhere in the

state) and level of education attained (till high school and above high school including trade, TAFE which stands for technical and further education and provides training for vocational occupations, or university).

Emotional response to cancer in family or community: Individual responses (Yes/No) to the question regarding the response to cancer in the community or family (Table 1) was explored. The objective was to gain better understanding of the approaches to consider for management of cancer in the Indigenous community, driven by the Aboriginal community. Apart from the list of emotions provided, there was an option to specify any other emotions identified. Data was descriptively analysed using SPSS (IBM; Version 27).

WHEN OTHERS IN YOUR FAMILY/COMMUNITY GET CANCER/ THE BIG C, DO YOU FEEL?		
ANGER	Yes	No
FRUSTRATION	Yes	No
SADNESS	Yes	No
GUILT	Yes	No
REVENGE	Yes	No
FEAR	Yes	No

Table 1: Question regarding the response to cancer in the community or family

Results: 1011 participants were recruited at baseline (February 2018 to January 2019), across eight sites in South Australia. This cohort represents 5% of Indigenous adults in South Australia eligible for recruitment in this study.

Of the 1011 participants, 998 responded to the question about how they felt about cancer in the family/community. Of the 988 participants more than half (66.6%) were females, and almost half (49.5%) were below the age of 37 years. Almost two-thirds (62.6%) resided in non-

metropolitan locations and 67.5% reported high school as the highest educational attainment. More than half reported to feeling Anger (58.2%) and 69% reported feelings of frustration. Most (90.8%) reported feeling sad, 26.6% felt guilt whilst 10.8% reported feelings of revenge on hearing of cancer in the family or community. Almost three-quarters (72.1%) reported feeling fear on hearing the diagnosis (Table 1).

Table 1: Frequency of responses recorded

	Responses	
	N	Percent
Anger	581	62.3%
Frustration	689	73.9%
Sadness	906	97.2%
Guilt	265	28.4%
Revenge	108	11.6%
Fear	720	77.3%

Figure 2: Graphical representation of the most frequently recorded responses

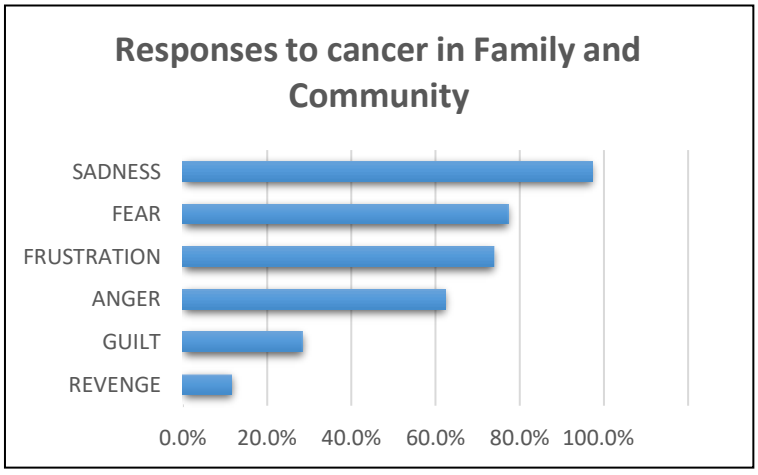
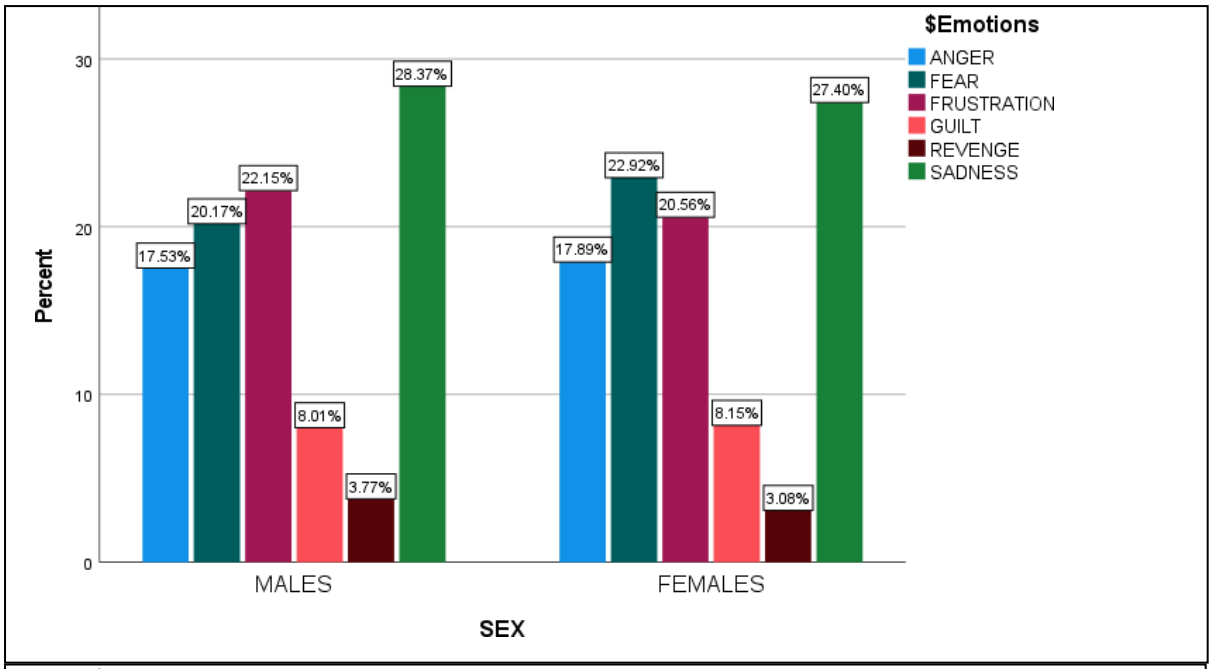


Figure 3: Graphical representation of gender and location specific responses to cancer in the family/community



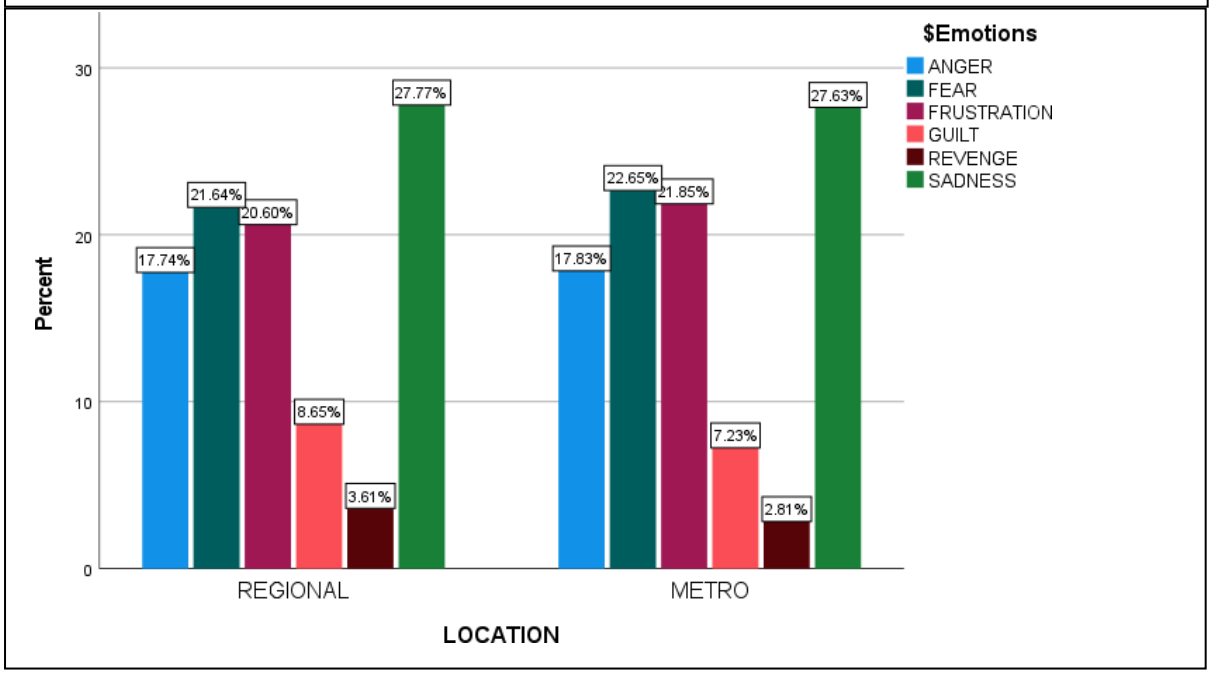


Table 3: Sociodemographic characteristics stratified by the emotional responses recorded

Characteristic	HPV-OPC study emotional response recoded (%, 95%CI)					
	Anger (N=581)	Frustration (N=689)	Sadness (N=906)	Guilt (N=265)	Revenge (N=108)	Fear (N=720)
Total (100)	58.2 (55.1-61.2)	69.0 (66.1-71.8)	90.8 (88.9-92.5)	26.6 (23.9-29.4)	10.8 (9.0-12.9)	72.1 (69.3-74.9)
Sex Male Female	32.0 (28.3-35.9) 68.0 (64.1-71.7)	34.1 (30.6-37.7) 65.9 (62.3-69.4)	33.2 (30.2-36.3) 66.8 (63.7-69.8)	32.1 (26.7-37.9) 67.9 (62.1-73.3)	37.0 (28.4-46.4) 63.0 (53.6-71.6)	29.7 (26.5-33.1) 70.3 (66.9-73.5)
Age ≥37 <37	49.1 (45.0-53.1) 50.9 (46.9-55.0)	50.2 (46.5-53.9) 49.8 (46.1-53.5)	49.7 (46.4-52.9) 50.3 (47.1-53.6)	46.4 (40.5-52.4) 53.6 (47.6-59.5)	39.8 (31.0-49.2) 60.2 (50.8-69.0)	51.7 (48.0-55.3) 48.3 (44.7-52.0)
Geographic Location Regional Metropolitan	61.8 (57.8-65.7) 38.2 (34.3-42.2)	60.5 (56.8-64.1) 39.5 (35.9-43.2)	62.0 (58.8-65.1) 38.0 (34.9-41.2)	66.0 (60.2-71.5) 34.0 (28.5-39.8)	67.6 (58.4-75.9) 32.4 (24.1-41.6)	60.8 (57.2-64.3) 39.2 (35.7-42.8)
Level of Education Till High school TAFE/University	67.6 (63.8-71.4) 32.4 (28.6-36.2)	67.5 (63.9-70.9) 32.5 (29.1-36.1)	68.2 (65.1-71.2) 31.8 (28.8-34.9)	67.5 (61.7-73.0) 32.5 (27.0-38.3)	72.2 (63.3-80.0) 27.8 (20.0-36.7)	67.5 (64.0-70.8) 32.5 (29.2-36.0)

**HPV-OPC – Human Papillomavirus - Oropharyngeal carcinoma study
CI- confidence intervals
TAFE – Provides training for technical education

Discussion

Cancer has substantial repercussions on an individual and their families (36),(37). It has been reported that significant emotional, social, physical and, spiritual changes occur in a family after a family member has been diagnosed with cancer (38). Green et al (26) described the

context of cancer as described by Indigenous participants. The most important factors identified were the experiences of racism (past and present), discrimination, Indigenous health disparities, mistrust in the healthcare system and different lifestyles. There was an unacceptable notion of generalizing all Indigenous peoples' life, culture and, circumstances (26).

The emotional cycle of cancer can be broadly divided into 3 stages; stage of diagnosis, stage of treatment and stage of recurrence. The stage of diagnosis and recurrence is most frequently associated with fear and sadness. Gorman and colleagues (36) explain the family's fears associated with cancer and elaborated on it in reference to the stage of diagnosis and recurrence. They indicated that fear can be multifactorial including a loss of their relationship, the loss of control, the fear of sorrow and, the fear of pain and suffering.

The following section discusses each emotion (Fear, Anger, Frustration, Guilt, Sadness and, Revenge) individually. The association of these emotions with cancer in the community or family, with any prior research in regards to Indigenous communities, is discussed.

Fear: The Recognition Phase of cancer (39), includes the individual's awareness about changes in their body which could indicate cancer, including abnormal growth, pain, or bleeding. Fear of cancer or previous cancer in the family/community can lead to a delay in acknowledging the changes and demotivate the patient to seek a diagnosis. This fear could bedue to financial limitations, fear of healthcare providers, fear of dependency, or fear of disfigurement (36). The roots of this fear are reinforced by avoidance of using the word – CANCER (40, 41). The fear of seeing a loved one in a vulnerable state has been associated with distress, fearing a change in personality and the dynamics of their relations (36). Partnersand spouses feel overwhelmed as they have not reflected what life together with illness and suffering would involve (42). A cancer diagnosis can either distance couples due to the stress on the relationship or can bring them closer together as a part of the survival struggle (37). Many Indigenous languages do not define the word "cancer" and are frequently associated with

bad spirits and negative energies (43). This adverse energy creates a fearful aura which is further fed into, by the scarce involvement of Indigenous peoples in health promotional activities and media awareness presentations (44). Green et al recorded the lack of open discussions about the 'C-Word' in Indigenous communities, which was associated with stigma and the large amount of stress (26). Cancer is often associated with feelings of shame which leads to a late diagnosis and a poorer prognosis(43). This highlights a large gap in communication about cancer and its management amongst Indigenous populations. The impact of institutional racism and intimidation of Indigenous patients due to 'cold' interactions with 'medical monsters' or the 'dominant white medical culture' further impedes successful engagement and instils fear (26). The impact of racism was voiced by a study by the Maori (27);

"*Our koros and our kuias* [elders]*; their mana* [status/authority] *gets tramped on. Their wishes don't get respected. If you are tūturu to your Māori-ness* [everything is subsumed by your Māori identity]*, you know that the whānau looks after their own. And when they are sick and they go to the hospital, that all goes out the window. It becomes, excuse me, the white man's rule. There is no negotiating. You do it this way or you get out. I don't get out. I got a mouth. And our old people, they don't want other people wiping their bums, washing them. That is what keeps their mana intact, having that respect. Their* [HCP] *job is to look after the tinana* [body], *but you need to look after the wairua* [spirit/soul] *too. Because that's what keeps the person going."*

Anger and Frustration: An initial period of ambiguity and doubt is frequently followed by extreme reactions of anger and frustration, eventually leading to psychological distress and disruption. The family/community may go through denial or they may blame others for this diagnosis (36). They may experience vulnerability with the conscious thought that this could happen to them. The inability of an individual to help or protect a loved one can create intense

vulnerability, helplessness and, frustration (36). Green et al (26) reported that health professionals do recognize the fear and anger amongst Indigenous patients and felt that one bad experience could be critical in defining the care journey for the entire family/community. The emotional frustration and anger can be inferenced from quotes of participants in various studies (26, 27);

"'And they said, "Oh, Aboriginal people don't burn when they have radiation". And that's an outright lie …Because I was burnt red raw from radiation (26)."

"We sat there absolutely petrified, waiting to squeeze every little bit of information they had in that little half an hour session. A secretary from upstairs came down twice to present some other patient's case. And it just broke… I was just angry after that. …I thought we were going to get their devoted attention (27)."

Other factors which precipitate feelings of frustration include disorder in daily chores such as sustaining a job, taking care of dependents and, other domestic errands (36). A loss of control surrounds the patient and the family, as they come to terms with the realization that there is nothing that they can do to stop the disease. This can spawn many emotions, with anger being the most common. This anger is often expressed to healthcare workers (physicians and nurses) for their incapability and inefficiencies (36). The loss of control and its associated anger also arises from other areas of patients' lives including loss of sleep, anxiety, conflicts within the family and disordered schedules.

Guilt: The most feared aspect of cancer for the patient and family is metastasis and recurrence. This is associated with depression, guilt, fear of death and anger. It has been observed that patients with recurrences lean towards less contact with family and loved ones due to the feelings of extensive strain on relationships and overwhelming changes in the emotional climate (45, 46). The patient feels constantly guilty of the emotional, physical, social and

financial drain caused to the family by their illness. Conversely, it has been observed that positive support from partners or families may result in heightened confidence among patients to fight the illness and relationships are stronger to face any new challenges. Thus, the perception and management of cancer in the family /community is a very important aspect, which controls the psychological balance of the patient (36). Guilt may be a cardinal feature of the caregiving experience, and to fully understand the implications of this complex phenomenon, more research is recommended.

*Sadness***:** There is a constant surge in the apprehensions regarding the loss of life which produce strong emotions, which all lead to intense sadness. The grieving process initiates with denial leading to anger, irritability and despair ending in sadness. It has been observed that the intensity of sadness increases if the family members protect themselves by avoidance or preoccupation (36). Acceptance and supporting the loved ones, regardless of age, is extremely important in this process (47). From an Indigenous perspective, it has been found that being away from one's own Country or traditional lands, as well as the likelihood of dying off Country, was a particular cause of sadness (26). Green et al found that all Indigenous participants reported intense grief and shock when they heard of cancer in their family or community (26).

Revenge: Studies have reported the correlational and causal role of anger in precipitating feelings of revenge (48-50). Anger is the most significant predictor of vengeance (51). In case of perceived injustices, there is a sense of morally appropriate anger that triggers feelings of revenge (52). Although there is limited literature which records the emotional feelings of revenge amongst community members or family members of cancer patients, it emerges as a possible consequence. This consequence can be explained by the feelings of intense anger and frustration felt by families which could promote feelings of revenge or vengeance as well.

Some useful interventions include assisting family/community in facing their loss, recognizing their struggles to support the patient, and ascertaining ways to affirm patients and families sense of control (36). It has been reported that family caregivers had improved mourning outcomes when they felt they had accomplished something to cherish such as providing comfort and compassion to their loved one (53). Australia's National Aboriginal and Torres Strait Islander Cancer Framework emphasizes the assessment of Indigenous understandings of care, to augment the capacity of cancer services (24). Community suggested solutions includedmore open conversations or yarns ('*Yarning*' is a popular term used for an Indigenous style of conversation and storytelling) (54) about the cancer journey and available resources and pathways (26). The appointment of Indigenous liaison officers or health workers was emphasized in one study (26) and suggested that it would enable the family to trust the system, voice their concerns and further facilitate relationships with the healthcare workforce.

There is an increase in the level of acknowledgment that diverse methods are required to effectively capture and appreciate the perspectives and perceptions of cancer among Indigenous communities (55-57). Despite the increase in awareness, there is limited pragmatic evidence regarding the best methodology to achieve desirable results. In general, measurement of Indigenous cancer patients' experiences is a complex process, and the additional aspects such as poor cancer outcome increase the challenge and urgency of the situation.

References:

1. Charles D. Spielberger ECR. Assessment of Emotions: Anxiety, Anger, Depression, and Curiosity. Applied psychology: Health and Well-being. 2009;1(3):271-302.

2. WHO. 2006.

3. Conte KP, Gwynn J, Turner N, Koller C, Gillham KE. Making space for Aboriginal and Torres Strait Islander community health workers in health promotion. Health Promot Int. 2020;35(3):562-74.

4. Taylor EV, Lyford M, Parsons L, Mason T, Sabesan S, Thompson SC. “We’re very much part of the team here”: A culture of respect for Indigenous health workforce transforms Indigenous health care. PLOS ONE. 2020;15(9):e0239207.

5. Gracey M, King M. Indigenous health part 1: determinants and disease patterns. Lancet (London, England). 2009;374(9683):65-75.

6. Cabinet. DotPMa. Closing the Gap Prime Minister's report 2020 2020.

7. McLennan W MR. The health and welfare of Australia's Aboriginal and Torres Strait Islander Peoples Canberra: Australian Bureau of Statistics. 1997.

8. Vos T, Barker B, Begg S, Stanley L, Lopez AD. Burden of disease and injury in Aboriginal and Torres Strait Islander Peoples: the Indigenous health gap. International journal of epidemiology. 2009;38(2):470-7.

9. Condon JR, Zhang X, Baade P, Griffiths K, Cunningham J, Roder DM, et al. Cancer survival for Aboriginal and Torres Strait Islander Australians: a national study of survival rates and excess mortality. Population health metrics. 2014;12(1):1.

10. Australia. AIoHaWC. Cancer in Aboriginal and Torres Strait Islander peoples of Australia: an overview. Cancer series no78. 2013.;Cat. no. CAN 75.

11. Sarfati D, Garvey G, Robson B, Moore S, Cunningham R, Withrow D, et al. Measuring cancer in indigenous populations. Annals of epidemiology. 2018;28(5):335-42.

12. Kingsley J, Townsend M, Henderson-Wilson C, Bolam B. Developing an exploratory framework linking Australian Aboriginal peoples' connection to country and concepts of wellbeing. Int J Environ Res Public Health. 2013;10(2):678-98.

13. Meiklejohn JA, Bailie R, Adams J, Garvey G, Bernardes CM, Williamson D, et al. “I’m a Survivor”: Aboriginal and Torres Strait Islander Cancer Survivors’ Perspectives of Cancer Survivorship. Cancer Nursing. 2020;43(2).

14. Shahid S, Durey A, Bessarab D, Aoun SM, Thompson SC. Identifying barriers and improving communication between cancer service providers and Aboriginal patients and their families: the perspective of service providers. BMC health services research. 2013;13(1):460.

15. Shahid S, Finn LD, Thompson SC. Barriers to participation of Aboriginal people in cancer care: communication in the hospital setting. The Medical journal of Australia. 2009;190(10):574-9.

16. Davy C, Kite E, Sivak L, Brown A, Ahmat T, Brahim G, et al. Towards the development of a wellbeing model for Aboriginal and Torres Strait Islander peoples living with chronic disease. BMC health services research. 2017;17(1):659.

17. Chynoweth J, McCambridge MM, Zorbas HM, Elston JK, Thomas RJS, Glasson WJH, et al. Optimal Cancer Care for Aboriginal and Torres Strait Islander People: A SharedApproach to System Level Change. JCO Glob Oncol. 2020;6:108-14.

18. Aspin C, Brown N, Jowsey T, Yen L, Leeder S. Strategic approaches to enhanced health service delivery for Aboriginal and Torres Strait Islander people with chronic illness: a qualitative study. BMC health services research. 2012;12:143.

19. Tam L, Garvey G, Meiklejohn J, Martin J, Adams J, Walpole E, et al. Exploring Positive Survivorship Experiences of Indigenous Australian Cancer Patients. Int J Environ Res Public Health. 2018;15(1):135.

20. Cavanagh BM, Wakefield CE, McLoone JK, Garvey G, Cohn RJ. Cancer survivorship services for indigenous peoples: where we stand, where to improve? A systematic review. Journal of cancer survivorship : research and practice. 2016;10(2):330-41.

21. Wotherspoon C, Williams CM. Exploring the experiences of Aboriginal and Torres Strait Islander patients admitted to a metropolitan health service. Australian health review : a publication of the Australian Hospital Association. 2019;43(2):217-23.

22. Shahid S, Finn L, Bessarab D, Thompson SC. 'Nowhere to room … nobody told them': logistical and cultural impediments to Aboriginal peoples' participation in cancer treatment. Australian health review : a publication of the Australian Hospital Association. 2011;35(2):235-41.

23. Tranberg R, Alexander S, Hatcher D, Mackey S, Shahid S, Holden L, et al. Factors influencing cancer treatment decision-making by indigenous peoples: a systematic review. Psycho-oncology. 2016;25(2):131-41.

24. Australia C. National Aboriginal and Torres Strait Islander Cancer Framework. Surry Hills, NSW, Australia. 2015.

25. Australia. C. National Aboriginal and Torres Strait Islander Cancer Framework 2015. Cancer Australia, Surry Hills, NSW Accessed 6 Dec 2018.

26. Green M, Anderson K, Griffiths K, Garvey G, Cunningham J. Understanding Indigenous Australians' experiences of cancer care: stakeholders' views on what to measure and how to measure it. BMC health services research. 2018;18(1):982.

27. Kidd J, Cassim S, Rolleston A, Chepulis L, Hokowhitu B, Keenan R, et al. Hā Ora: secondary care barriers and enablers to early diagnosis of lung cancer for Māori communities. BMC Cancer. 2021;21(1):121.

28. Risetevski E TS, Kingaby S, Nightingale C and Iddawela M. Understanding Aboriginal Peoples' Cultural and Family Connections Can Help Inform the Development of Culturally Appropriate Cancer Survivorship Models of Care JCO Glob Oncol. 2020;6:124-32.

29. Litzelman K, Kent EE, Rowland JH. Interrelationships Between Health Behaviors and Coping Strategies Among Informal Caregivers of Cancer Survivors. Health education &

behavior : the official publication of the Society for Public Health Education. 2018;45(1):90-100.

30. Park CL, Iacocca MO. A stress and coping perspective on health behaviors: theoretical and methodological considerations. Anxiety, stress, and coping. 2014;27(2):123-37.

31. Daly J, Sindone AP, Thompson DR, Hancock K, Chang E, Davidson P. Barriers to participation in and adherence to cardiac rehabilitation programs: a critical literature review. Progress in cardiovascular nursing. 2002;17(1):8-17.

32. James EL, Stacey F, Chapman K, Lubans DR, Asprey G, Sundquist K, et al. Exercise and nutrition routine improving cancer health (ENRICH): the protocol for a randomized efficacy trial of a nutrition and physical activity program for adult cancer survivors and carers. BMC public health. 2011;11:236.

33. Martire LM, Lustig AP, Schulz R, Miller GE, Helgeson VS. Is it beneficial to involve a family member? A meta-analysis of psychosocial interventions for chronic illness. Health psychology : official journal of the Division of Health Psychology, American Psychological Association. 2004;23(6):599-611.

34. Weaver KE, Rowland JH, Augustson E, Atienza AA. Smoking concordance in lung and colorectal cancer patient-caregiver dyads and quality of life. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2011;20(2):239-48.

35. Jamieson LM, Garvey G, Hedges J, Leane C, Hill I, Brown A, et al. Cohort profile: indigenous human papillomavirus and oropharyngeal squamous cell carcinoma study - a prospective longitudinal cohort. BMJ Open. 2021;11(6):e046928.

36. Gorman LM. Psychosocial Impact of Cancer on the Individual, Family, and Society. Psychosocial Nursing Care Along the Cancer Continuum. 2018(3):1-21.

37. Glajchen M. The emerging role and needs of family caregivers in cancer care. The journal of supportive oncology. 2004;2(2):145-55.

38. Northouse L. Helping families of patients with cancer. Oncology nursing forum. 2005;32(4):743-50.

39. Nail LM. I'm coping as fast as I can: psychosocial adjustment to cancer and cancer treatment. Oncology nursing forum. 2001;28(6):967-70.

40. Holland JC. History of psycho-oncology: overcoming attitudinal and conceptual barriers. Psychosomatic medicine. 2002;64(2):206-21.

41. Holland JC. American Cancer Society Award lecture. Psychological care of patients: psycho-oncology's contribution. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2003;21(23 Suppl):253s-65s.

42. Shell JA, & Kirsch, S.). . Psychosocial issues, outcomes, and quality of life. Oncology nursing. 2001;4: 948–72.

43. J P. There’s no aboriginal word for cancer. Origins. 2013;1 22 - 3.

44. Treloar C, Gray R, Brener L, Jackson C, Saunders V, Johnson P, et al. Health literacy in relation to cancer: addressing the silence about and absence of cancer discussion among Aboriginal people, communities and health services. Health & social care in the community. 2013;21(6):655-64.

45. Mahon SM, Casperson DS. Psychosocial concerns associated with recurrent cancer. Cancer practice. 1995;3(6):372-80.

46. R DBaS. Supporting families in Palliative Care. supporting Families in Palliative care - Social Aspects of Care

47. Hames CC. Helping Infants and Toddlers When a Family Member Dies. Journal of Hospice & Palliative Nursing. 2003;5(2).

48. Barber L, Maltby J, Macaskill A. Angry memories and thoughts of revenge: The relationship between forgiveness and anger rumination. Personality and Individual Differences. 2005;39:253-62.

49. Eisenberger R, Lynch P, Aselage J, Rohdieck S. Who takes the most revenge? Individual differences in negative reciprocity norm endorsement. Personality & social psychology bulletin. 2004;30(6):787-99.

50. Lerner J, Goldberg J, Tetlock P. Sober Second Thought: The Effects of Accountability, Anger, and Authoritarianism on Attributions of Responsibility. Personality and Social Psychology Bulletin. 1998;24:563-74.

51. Roseman IJ, Wiest C, Swartz TS. Phenomenology, behaviors, and goals differentiate discrete emotions. Journal of Personality and Social Psychology. 1994;67(2):206-21.

52. Tripp TM BR. “Righteous” anger and revenge in the workplace: the fantasies, the feuds, the

forgiveness. International Handbook of Ange. 2010;ed. M Potegal, G Stemmer, C Spielberger:pp. 413–31.

53. Koop PM, Strang VR. The bereavement experience following home-based family caregiving for persons with advanced cancer. Clinical nursing research. 2003;12(2):127-44.

54. Laycock A wWD, Harrison N, Brands J. Researching Indigenous health: a practical guide for researchers. . The Lowitja Institute, Melbourne. 2018.

55. Information. BoH. Patient perspectives – hospital care for Aboriginal people. Sydney (NSW). 2016.

56. Green M, Cunningham J, O'Connell D, Garvey G. Improving outcomes for Aboriginal and Torres Strait Islander people with cancer requires a systematic approach to understanding patients' experiences of care. Australian health review : a publication of the Australian Hospital Association. 2017;41(2):231-3.

57. Yerrell PH, Roder D, Cargo M, Reilly R, Banham D, Micklem JM, et al. Cancer Data and Aboriginal Disparities (CanDAD)-developing an Advanced Cancer Data System for Aboriginal people in South Australia: a mixed methods research protocol. BMJ open. 2016;6(12):e012505-e.

End of Published Pape

SECTION F: FUTURE DIRECTIONS

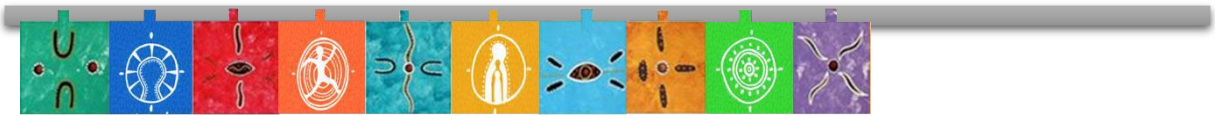
Overview of Section F

This section comprises a discussion about the use of a non-invasive, accurate and sensitive tool for oral cancer detection. Earlier detection of oral cancer can improve prognosis and quality of life. Poorer cancer outcomes of Indigenous populations compared with non-Indigenous outcomes are partially due to inadequate access to cancer awareness, screening and treatment services. The next step of this research leads into a phase of clinical examinations of the participants of the HPV-OPC study.

This chapter discusses the diagnostic accuracy of Confocal Laser Endomicroscopy for detection of oral squamous cell carcinoma.

10

Diagnostic Accuracy of Confocal Laser Endomicroscopy for the Diagnosis of Oral Squamous Cell Carcinoma: A Systematic Review and Meta-Analysis



10.1 PREFACE AND LINK TO PROJECT

The study (Study 7) presented in this Chapter is the only Chapter in this section that addresses the final objective of this thesis. One of the reasons for lower cancer screening and delayed diagnosis in Indigenous communities is the diminished access to cancer awareness, screening and treatment services. This highlights the need for a convenient, portable and culturally safe tool, which can be used for cancer screening in remote areas.

The next step of the HPV-OPC study leads to a phase of clinical examinations of the participants recruited as part of the study. This Chapter discusses the diagnostic accuracy of Confocal Laser Endomicroscopy which is a non-invasive and transportable tool used for detection of oral squamous cell carcinoma. The highlight of this tool its convenient portability for screening at remote locations.

10.2 PUBLICATION DETAILS

This paper is under review in the Journal of Oral Oncology as: Sethi S, Ju X, Logan R, Sambrook P, McLaughlin R, Jamieson L. Diagnostic Accuracy of Confocal Laser Endomicroscopy for the Diagnosis of Oral Squamous Cell Carcinoma: A Systematic Review and Meta-Analysis. J Oral Oncol (Under review; submission date)

10.3 HIGHLIGHTS

- Confocal laser endomicroscopy (CLE) shows high sensitivity and specificity for diagnosing oral squamous cell carcinoma.
- Transference of the first experimental results of CLE in the human oral cavity into an effective and evidence based clinical setting is recommended

10.4 STATEMENT OF AUTHORSHIP

Statement of Authorship

Title of Paper	Diagnostic Accuracy of Confocal Laser Endomicroscopy for the Diagnosis of Oral Squamous Cell Carcinoma: A Systematic Review and Meta-Analysis
Publication Status	☐ Published ☐ Accepted for Publication ☑ Submitted for Publication ☐ Unpublished and Unsubmitted work written in manuscript style
Publication Details	Sethi S, Ju X, Logan R, Sambrook P, McLaughlin R, Jamieson L. Diagnostic Accuracy of Confocal Laser Endomicroscopy for the Diagnosis of Oral Squamous Cell Carcinoma: A Systematic Review and Meta-Analysis. Oral Oncology (Under Review)

Principal Author

Name of Principal Author (Candidate)	Sneha Sethi
Contribution to the Paper	Conceiving of Research Question Data extraction, appraisal and analysis Manuscript Writing Editing and Revisions Paper submission for pubmication Correspondece with Editors in the publication process
Overall percentage (%)	75%
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.
Signature	Date 15/09/2021

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);
ii. permission is granted for the candidate in include the publication in the thesis; and
iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Xiangqun Ju
Contribution to the Paper	Orientation on formulation of Research question Revision of Methodology Input in theory application Input in Interpretation of results Revision of Manuscript
Signature	Date 15/09/2021

Name of Co-Author	Richard Logan
Contribution to the Paper	Revision of Methodology Input in theory application Input in Interpretation of results Revision of Manuscript
Signature	Date 20 Sept 2021

Name of Co-Author	Paul Sambrook		
Contribution to the Paper	Revision in Methodology Input in interpretation of results Revison and editing of manuscriptype		
Signature		Date	15/09/2021

Name of Co-Author	Rober McLaughlin		
Contribution to the Paper	Revision in Methodology Input in interpreation of results Revision and editing of manuscript		
Signature		Date	15/09/2021

Name of Co-Author	Lisa Jamieson		
Contribution to the Paper	Orientation on formulation of Research question Revision of Methodology Input in theory application Input in Interpretation of Results Revison of Manuscript		
Signature		Date	15/09/2021

10.5 PUBLICATION

Title: Diagnostic Accuracy of Confocal Laser Endomicroscopy for the Diagnosis of Oral Squamous Cell Carcinoma: A Systematic Review and Meta-Analysis

Sneha Sethi1*, Xiangqun Ju1, Richard Logan2, Paul Sambrook2, Robert McLaughlin3,4,5, Lisa Jamieson1

1. Australian Research Centre for Population Oral Health, Adelaide Dental School, Faculty of Health and Medical Sciences, University of Adelaide, Adelaide, South Australia, Australia

2. Adelaide Dental Hospital, Faculty of Health and Medical Sciences, University of Adelaide, Adelaide, South Australia, Australia

3. School of Biomedicine, Faculty of Health and Medical Sciences, University of Adelaide, Adelaide, South Australia, Australia.

4. Australian Research Council Centre of Excellence for Nanoscale Bio-photonics, The University of Adelaide, Adelaide, South Australia, Australia

5. Institute of Photonics and Advanced Sensing, The University of Adelaide, Adelaide, South Australia, Australia

Abstract

Background

Advances in treatment approaches for patients with oral squamous cell carcinoma (OSCC) have been unsuccessful in preventing frequent recurrences and distant metastases, leading to a poor prognosis. Early detection and prevention enable an improved 5-year survival and better prognosis. Confocal laser Endomicroscopy (CLE) is a non-invasive imaging technique that could enable an earlier diagnosis and possibly help in reducing unnecessary invasive surgical procedures.

Objective

To present an up to date systematic review and meta-analysis assessing the diagnostic accuracy of CLE in diagnosing OSCC.

Materials and Methods

PubMed, Scopus, and Web of Science databases were searched up to June 30, 2021, to collect articles concerning diagnosis of OSCC diagnosis through CLE. Screening, data extraction and appraisal was done by two reviewers. The quality of the methodology followed by the studies included in this review was assessed using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool. A random effects model was used for the meta-analysis.

Results

Six studies were included, leading to a total number of 361 lesions in 213 patients. The pooled sensitivity and specificity were 95% (95% CI, 92%-97%; I^2 = 77.5%) and 93% (95% CI, 90%–95%; I^2 = 68.6%); the pooled positive and negative likelihood ratios were 10.85 (95% CI, 5.4–21.7; I^2 = 55.9%) and 0.08 (95% CI, 0.03–0.2; I^2 = 83.5%); and the pooled diagnostic odds ratio was 174.45 (95% CI, 34.51–881.69; I^2 = 73.6%). Despite the heterogeneity and risk of bias, this study demonstrates that CLE, through its high sensitivity and specificity, may have a significant clinical impact on the diagnosis of OSCC.

Conclusions:

This review indicates an exceptionally high sensitivity and specificity of CLE for diagnosing OSCC. Whilst it is a promising diagnostic instrument, the limited number of existing studies and potential risk of bias of included studies do not allow us to draw firm conclusions. A conclusive inference can be drawn when more studies, possibly with homogeneous methodological approach, are performed.

Keywords:

Oral squamous cell carcinoma, diagnostic test accuracy, confocal laser endomicroscopy, systematic review, meta-analysis

Highlights

- Confocal Laser Endomicroscopy (CLE) has very high sensitivity and specificity for diagnosing Oral squamous cell carcinoma (OSCC).
- Transference of the first experimental results of CLE in the human oral cavity into an effective and evidence based clinical setting is recommended.
- A definitive conclusion could only be drawn when a higher number of studies, possibly with homogeneous methodological approach, will be available.

Introduction

Head and Neck squamous cell carcinoma is the sixth most common cancer (1) in the world, contributing towards 5% of all human malignancies (2). Ten percent of all cancer cases are neoplasms of the head and neck area, of which more than 90 % are classified as oral squamous cell carcinoma (OSCC) (3). The majority of OSCC patients are treated by a combination of surgery, radiation and chemotherapy (4). Despite advances in treatment strategies, patients with OSCC suffer from a poor prognosis due to frequent recurrences and distant metastases (5). Early detection and prevention are crucial factors in achieving better prognosis of OSCC with an improved 5-year survival (6).

OSCC has a multifactorial aetiology, including tobacco consumption, alcohol habits and viral (Human papillomavirus) infections (7). Field cancerization is the most acceptable theory among researchers and clinicians, which explains frequent recurrences and metastases in OSCC (8). Slaughter et al (9), defined field cancerization as a pre-neoplastic mucosal area composed of epithelial cells with genetic or epigenetic changes beyond the original invasive malignancy, resulting in patients having several malignancies in various stages of development. Premalignant lesions of the oral cavity include leukoplakia, oral submucous fibrosis, erythroplakia, are characterised by white or red patches on the oral mucosa with epithelial changes ranging from hyperplasia to carcinoma in situ (10). The malignant transformation rate of leukoplakia ranges from 0.13 to 34% (11) and the transformation rate for erythroplakia ranges from 14% to 50% (12). Due to field cancerization, it is hypothesized that the entire oral mucosa will be exposed to the carcinogen, causing widespread premalignant and malignant changes (9). This situation represents a dilemma to the surgeon and diagnostic clinician regarding the resection margins and treatment regimens as complete resection of the tumour is essential for a good prognosis (13). This emphasizes the need for an instrument that enables the evaluation of dysplastic lesions in-vivo, preventing the need for wide spread preventive excision and avoidable invasive ex-vivo histopathology evaluation.

The inability to clearly define surgical margins intraoperatively in OSCC patients are the number one reason for recurrence of primary tumours and leading to a debilitating recurrence and associated

metastasis (14). The current practices which help in determining surgical margins include visualisation, palpation or frozen section histopathology (15). Although frozen sections are accurate, they are associated with multiple drawbacks, including compromising the tissue integrity and being time consuming (16). Avoiding unnecessary resection of healthy tissues is of utmost importance to the surgeons, due to the functional limitations post-operatively and severe impact on the quality of life of the patient (17, 18). This limitation also supports the requirement of an explicit and correct evaluation of the effected oral tissues preceding surgical resection.

An ideal solution to these problems would-be real-time histological evaluation by an instrument which is non-invasive, time efficient and sensitive enough to replace the gold standard of histopathology. This concept has been previously explored using narrow-band imaging (19, 20), autofluorescence imaging (21, 22), computed tomography (23) and confocal imaging (24). The later study was done with a handheld confocal laser endomicroscope comprising of a bundle fibre probe (Manua Kea Cellvizio) with IV fluorescein as the fluorescent dye. This technique allowed efficient visualization of the epithelial architecture with a fluorescent contrast on the intraoperative display (25). A fluorescent contrast agent intensifies the contrast of cells, which are highlighted by a blue laser. Additionally, the laser is used for structural information of the tissue. CLE aka "*optical biopsy*" is used to provide the surgeon with real-time cellular resolution digital images (1µm to a 1000-fold magnification) during surgical procedures, allowing effective analysis of the surgical margins and ensuring improved precision in determination of tumour resection margins and preventing recurrence. This medical imaging modality enables an in vivo diagnosis and images can be acquired almost indefinitely whilst avoiding any iatrogenic harm to the patient.

Previously, CLE has shown effective imaging whilst diagnosing gastrointestinal neoplasia's including Barrett's oesophagus (26, 27) , intraepithelial neoplasia's of the colorectal tract (28, 29) , pre-neoplastic and neoplastic lesions of the cervical epithelium (30, 31), neoplastic lesions involving the bronchial epithelium (32-34), neoplastic lesions of the urothelial epithelium (35, 36) and lesions of the brain or spinal cord (37-39). The first report of CLE in the head and neck region, along with morphological correlations with corresponding H&E stained tissue sections, was described in 1999 (40), followed by many in-vivo and in-vitro studies (41-49)

To formulate comprehensive and conversant evidence-based suggestions for the coherent use of CLE, a systematic review and meta-analysis was designed, to assess the precision in the diagnosis of OSCC using histopathology as the reference standard.

Materials and Methods

A systematic review and meta-analysis was performed and the results were reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (50). Modifications were made as to adhere to the recommendations for reviewing diagnostic test accuracy reports (51). The review protocol was registered in the PROSPERO International Prospective Register of Systematic Reviews.

Study Objective and Definition of Reference Standard

A PICO (population, intervention, comparison, and outcome) strategy was implemented for the search (52). The population comprised of OSCC patients, OSCC can be defined as squamous cell carcinomas in the oropharynx, hypopharynx and oral cavity including tongue, palate etc. The intervention used was the use of CLE for diagnosis of OSCC. Outcome measures were true positives (TP), false positives (FP), true negatives (TN), and false negatives (FN) in detection of OSCC using histology as the reference standard. A diagnosis subsequent to histopathological examination of an incisional or excisional biopsy specimen was considered. The study design had no limitations, as long as original data was specified. The main objective of this systematic review and meta-analysis was to assess the accuracy of CLE for the diagnosis of OSCC.

Literature Search Strategy

Block search was carefully chosen as search strategy, as it accommodated the PICO approach. One reviewer (SS) searched the following databases from inception till 30 July 2021: PubMed (keywords "(oral squamous cell carcinoma)" OR "(Oral Cancer)" AND "(confocal microscopy"), Web of Science (keywords "TS = (confocal microscopy AND oral squamous cell carcinoma or Oral Cancer) Timespan: All years. Indexes: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC.") and Elsevier SCOPUS (keywords "TITLE-ABS-KEY ("confocal microscopy" AND "squamous cell carcinoma" OR "(Oral Cancer)"). All references were imported and deduplicated using the reference manager EndNote (version X9, 1988–2021 Thomson-Reuters).

To assess the applicability of studies, two reviewers (SS and XJ) independently screened all retrieved articles by titles first followed by abstracts to establish their relevance. Full-text recovery and analysis were done only for potentially eligible articles. Disagreements were settled through discussion with a third reviewer (LJ).

Inclusion and Exclusion Criteria

The established eligibility criteria were: (1) CLE device used in the study should be based on the principle of Fluorescent Laser Endomicroscopy only; (2) the investigated lesions were OSCCs (any histopathological subtype); (3) the reference standard was a histopathological diagnosis of OSCC

following the examination of the incisional or excisional biopsy specimen; (4) Only human studies were included; (5) No case reports or reviews were included; (6) Only articles written in English were taken into account for inclusion.

We excluded from the analysis: (1) all studies using Reflectance Confocal Microscopy were excluded; (2) all basal cell carcinomas or corneal/optical epithelial tumours were excluded; (3) all studies based on cytological smears were excluded; (4) no animal-based models or trials were included; (5) studies where full-text and recovery was not possible, even after searching the available medical databases and/or contacting the corresponding authors. Studies thought to include overlapping populations were also excluded, keeping only the one with the largest number of participants. Additionally, the reference list of each study was checked to identify further relevant articles that may have been overlooked during initial screening.

Data extraction

One reviewer (SS) extracted the data from the included studies into a predefined form, validated by another reviewer (XJ). The following parameters were extracted: the name of the first author, year of publication, country, tumour sites (percent frequency), number of Reviewers validating the CLE device, fluorescent agent used, total number of patients and lesions, patient gender and age (mean/median, years), sensitivity of instrument, specificity of instrument and, confocal criteria employed for the diagnosis of OSCC.

Risk of Bias

Risk of bias and quality of included studies was evaluated using the Quality Assessment of Diagnostic Accuracy Studies) QUADAS-2 checklist for primary studies assessing the diagnostic accuracy in four KEY domains; Patient Selection, Index Test, Reference Standard, and Flow and Timing (53). All 4 domains are appraised for risk of bias, and only the first three domains are appraised for applicability concerns. The risk of bias was assessed to be either high, low or unclear based on indicating questions: 1) whether the patient selection was a consecutive or random sample of patients enrolled; 2) if a threshold for index-test was prespecified; 3) if the reference standard was more likely to correctly diagnose OSCC; 4) and if there was an appropriate interval between index test and reference standard.

Statistical Analysis and Meta-Analysis

Two-by-two tables were constructed for each CLE-based diagnosis of OSCC against histopathology from incisional or excisional biopsy specimens and sensitivity, specificity and their 95% confidence intervals were visually represented using forest plots. Diagnostic accuracy in terms of sensitivity,

specificity, and diagnostic odds ratio with 95% confidence intervals was evaluated on the basis of TP, FP, TN, and FN extracted from each of the included studies.

Sensitivity was defined as the proportion of patients, correctly identified by CLE as having OSCC, and specificity as the proportion of patients, correctly identified on radiology as not having OSCC. Diagnostic odds ratio was defined as the odds of the CLE diagnosis being positive for a patient having OSCC relative to the odds of the CLE test being positive for patients not having OSCC. A bivariate model (hierarchical logistic regression) for the meta-analysis of sensitivity and specificity was designed (54) and the HSROC (Hierarchal summary receiver operating characteristic) curve was created. The HSROC curve graphically represents sensitivity versus specificity and provides information regarding the overall test performance across different thresholds. This model accounted for both the within- and between-study variability.

Heterogeneity is calculated as Higgins I^2, where I^2=0% indicates no observed heterogeneity and I^2>50% is categorised as substantial heterogeneity. Heterogeneity is a prominent attribute observed in almost all meta-analyses of diagnostic accuracy tests, which can be explained by index test efficiency variation due to diverse indicative diagnostic thresholds. We were not able to statistically analyse sources of heterogeneity, as subgroups were too small (two or three studies per group).

Data organization and statistical analyses was performed using the software packages STATA (v15.0; StataCorp LP, Texas, USA), MetaDisc (v1.4; Unidad de Bioestadistica Clinica—Hospital Ramon y Cajal, Universidad Complutense, Madrid, Spain) and Review Manager (v5.3; Nordic Cochrane Center, Copenhagen, Denmark).

Results

Literature Search Results

The initial database search identified a total number of 2,095 of articles. After removal of duplicates, only 1,554 remained. After title and abstract evaluation 1,509 items were excluded and only 45 were selected for full-text retrieval and analysis. Thirty-nine articles were excluded based on full-text analysis illustrated in Figure 1. Six studies totalling a number of 361 lesions in 213 patients were included in the final analysis (24, 55-59). Study characteristics are summarized in Table 1.

Figure 1 – Screening process and results. Oral squamous cell carcinoma (OSCC)

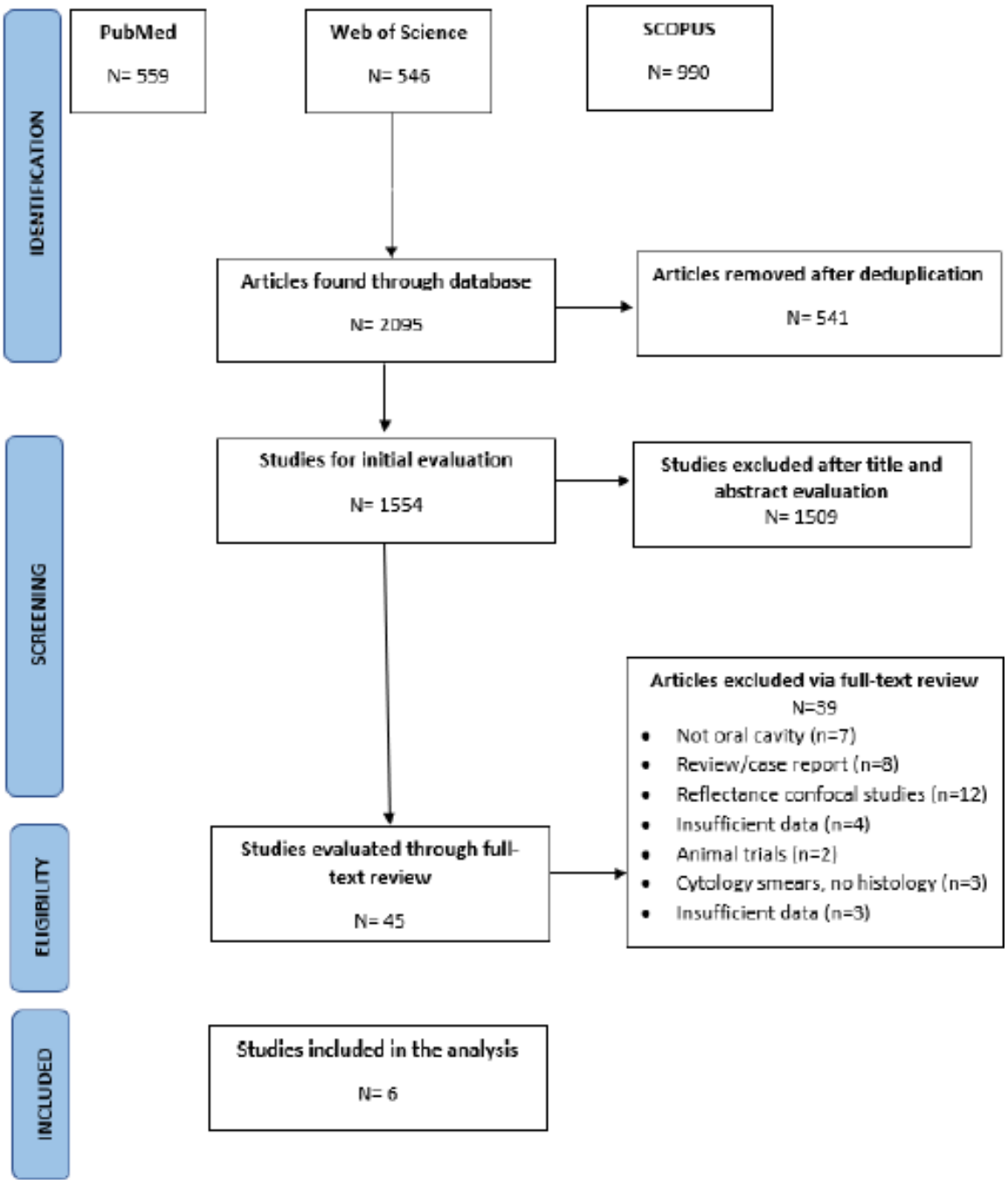


Table 1: Characteristics of included studies

Year	Author	Country	Site distribution	Examination setting	NO. of reviewers	CLE device	Fluorescent agent used	Total patients	Total sites	Patient gender (%) and age (mean/Median)	Reference
2021	Dittberner A, et al.	Germany	oropharynx (52.9%), oral cavity (35.3%), and hypopharynx (11.8%).	In vivo	2	CONVIVO, Carl Zeiss AG, Oberkochen, Germany	Fluorescein	13	30	Mean age- 61.9 years M- 69% F- 31%	conventional histopathology
2020	Shinohara S, et al	Japan	Hypopharynx (30%), Larynx (10%) Lower gingiva (20%), Tongue (20%), oropharynx (20%)	Ex vivo	ns	FIGH-300S or FIGH 350S, Fujikura or HDIG, Sumita	Acriflavine	10	10	Mean age- 67.7 years M- 80% F- 20%	conventional histopathology
2020	Shavlokhova V, et al.	Germany	Lip (7%), Palate (18%), Tongue (37%), Buccal Mucosa (15%), Floor of the mouth (23%)	Ex vivo	3	Vivascope 2500 Multilaser, Lucid Inc., Rochester, New York	Acridine Orange	70	70	Mean age- 68.7years M- 52.2% F- 47.8%	conventional histopathology
2016	Oetter et al	Germany	NS	In vivo	6	Cellvizio, Mauna Kea Technologies, Paris, France	fluorescein Alcon	NS	95	NS	conventional histopathology
2016	Linxweiler M et al,	Germany	tonsil cancer (26%), tongue base cancer (24%), hypopharyngeal cancer (15%), tongue cancer (10%), cancer of the soft palate (8%), cancer of the pharyngeal wall (7%), cancer of the floor of the mouth (6%), cancer of the buccal mucosa (3%)	Ex vivo	12	Cellvizio system (Mauna Kea Technologies, Paris, France	acriflavine hydrochloride	99	185	NS	conventional histopathology
2014	Nathan C et al	USA	Tongue (66.6%), Tonsil (4.7%), Vocal cord (14.2%), epiglottis (4.7%), floor of mouth (4.7%), retromolar triangle (4.7%)	In vivo	4	CellVizio; Mauna Kea Technologies, Paris, France	fluorescein Alcon	21	21	Mean Age- 64.2 years M- 47.6% F- 52.3%	conventional histopathology

*Abbreviations: - CLE- Confocal Laser Endomicroscopy, M – Males, F- Females, NS- Not Specified

Two out of the six included studies did not specify the patient details of mean age, number of males and females. The average percent of males and females across the remaining four studies were 62.2% and 37.8% respectively. The manufacturer of the CLE devices CellVizio, Vivascope 2500, FIGH-300S and CONVIVO was Mauna Kea Technologies (Paris, France), Lucid Inc. (Lucid Technologies, Henrietta, NY, USA), Fujikura or HDIG (Sumita) and Carl Zeiss AG (Oberkochen, Germany) respectively. The majority of studies were carried out in Germany. One study did not specify the site of OSCC in oral cavity (56). Confocal criteria for OSCC diagnosis varied considerably between studies (Table 2).

Table 2: Criteria for the diagnosis of oral squamous cell carcinoma in the included studies.

Author, Year, [Reference]	Laser Confocal Endoscopy Microscopic Criteria
Dittberner, A, 2021 (59)	Chronic inflammation, Dysplasia-free normal tissue, No to severe artefact classification, tissue architecture, cell morphology, fluorescence leakage, and the vessels.
Shinohara S, et al 2020 (58)	uniformity of nuclear size and shapes, cell density, nuclei and cytoplasm of cells
Shavlokhova V, 2021 (57)	disturbed polarity of the basal cells, basal cell hyperplasia, irregular epithelial stratification or disturbed maturational sequence, cellular pleomorphism/ anisocytosis, nuclear hyperchromatism, prominent nucleoli, intraepithelial keratinization, increase in nuclear cytoplasmic ratio
Oetter et al, 2016(56)	Homogeneity, Intercellular gaps, Cell morphology, Fluorescein leakage, Vessel morphology
Linxweiler M et al, et al 2019 (55)	variable cellular morphology, lack of cytoplasmic membranes, and a hazy, moth-eaten appearance.
Nathan C et al, 2014 (24)	normal or non-dysplasia, dysplasia, or cancer.

Risk of bias and Quality Assessment of Study Reports

The results of the methodological quality assessment of the studies are illustrated in Table 3.

Table 3: Methodological assessments using QUADAS-2 tool. Each domain is assessed for risk of bias and first three for their applicability concerns

Studies	Domain 1 Patient Selection		Domain 2 Index Test(s)		Domain 3 Reference Standard		Domain 4 Flow and Timing	Total Score
	Risk of Bias	Applicability Concerns	Risk of Bias	Applicability Concerns	Risk of Bias	Applicability Concerns	Risk of Bias	
Dittberner A, et al.	Low	Low	Low	Low	Low	Low	Low	0
Shinohara S, et al	low	unclear	high	Low	High	High	Low	7
Shavlokhova V, et al.	low	low	Low	unclear	Low	Low	High	3
Oetter et al	unclear	low	Low	Low	Low	Low	High	3
Linxweiler M et al,	low	high	unclear	Low	Low	Low	Low	3
Nathan C et al	low	low	Low	unclear	Low	Unclear	High	4

*(low – low risk (0 points), high – high risk (2 points) or unclear – unclear risk (1 point))

The included studies exhibited low or unclear risk for bias and applicability concerns in all domains. One study (16.66%) had an unclear (n = 1) risk of bias concerning patient selection indeterminate patient selection procedure. Five studies fully described the patient selection protocol. One study presented high and uncertain applicability concerns owing to restrictions applied to the studied population (including lesions of suspected premalignancy and malignancy) and inclusion of the contralateral oral mucosa of patients, which overlooks the concept of field cancerization and applicability of the tool.

Two out of the six included studies had a high or unclear risk of bias concerning the index test mostly due to the blinding of investigators to patient characteristics. Most of the studies had low applicability concerns in the index test domain due to clear demarcation of malignant changes in the observed epithelial cells.

Five of the included studies had a low risk of bias regarding the use of the reference standard due to clearly defined histopathological and confocal criteria, only one study had no clear diagnostic criteria and were at high risk of bias due to inadequate referencing standards. Regarding applicability concerns of the reference standard, only one study had a high risk owing to the use of expert clinical diagnosis as a reference standard, while one study did not specify the pathologists' experience level.

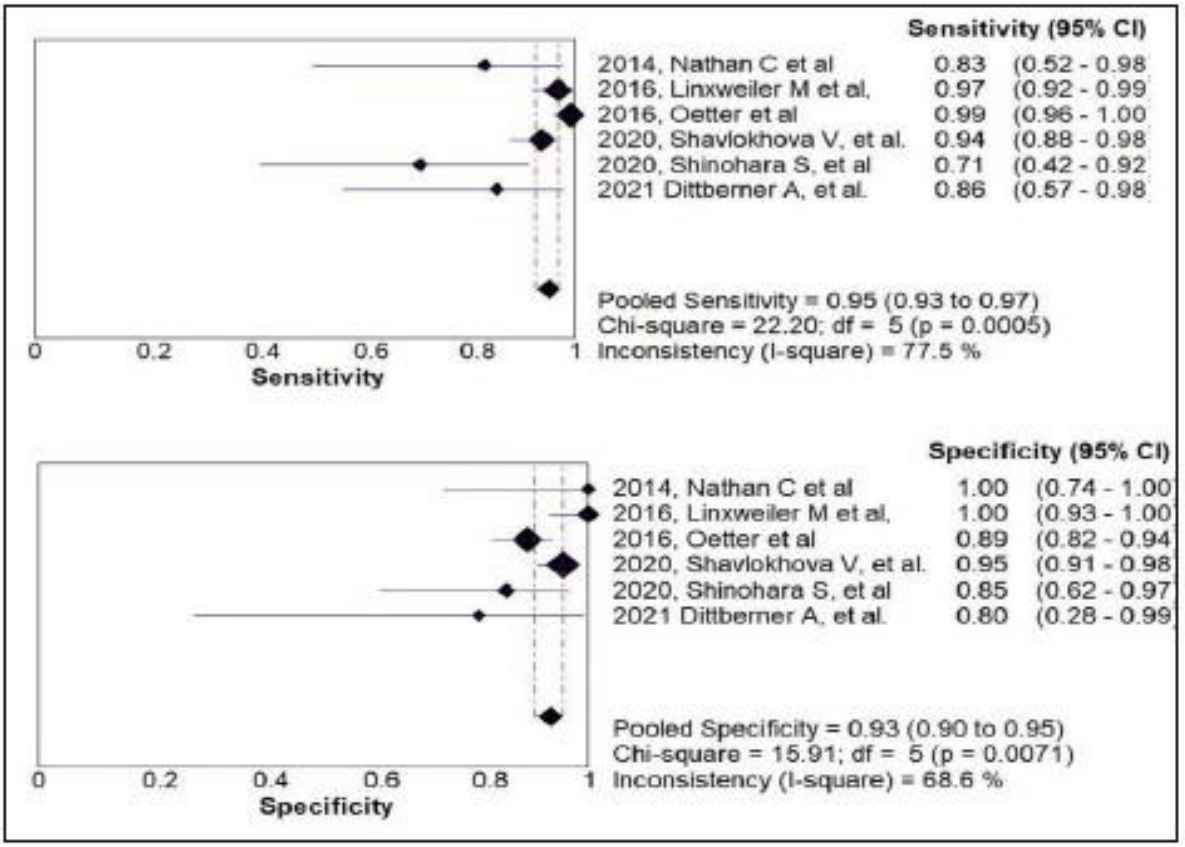
For the domain of flow and timing, according to the QUADAS-2 tool, three studies had a high risk of bias as these studies included a fair number of all benign and suspected dysplastic lesions.

Diagnostic Accuracy of CLE and Meta-Analysis

Whilst there are limitations to the conclusions that be drawn from a meta-analysis, the meta-analysis does give a general overview of the calculated sensitivity and specificity of any confocal microscope in different situations. Although, the studies used dissimilar tools in different settings, the actual point estimates of sensitivity and specificity depict 'threshold effect' in diagnostic clinical research.

All six studies were included in the meta-analysis. The results of the meta-analysis are reported but with its limitations, and caution against variation and potential biases. Sensitivity ranged from 71.4% to 99.3%, while specificity ranged from 80% to 100%. The pooled sensitivity and specificity values were 95% (95% CI, 92.9%–97%; $I^2 = 77.5\%$) and 93% (95% CI, 90%–95%; $I^2 = 68.6\%$). The distributions of CLE sensitivity and specificity and their summary values for the diagnosis of OSCC in the included studies is represented in Figure 2.

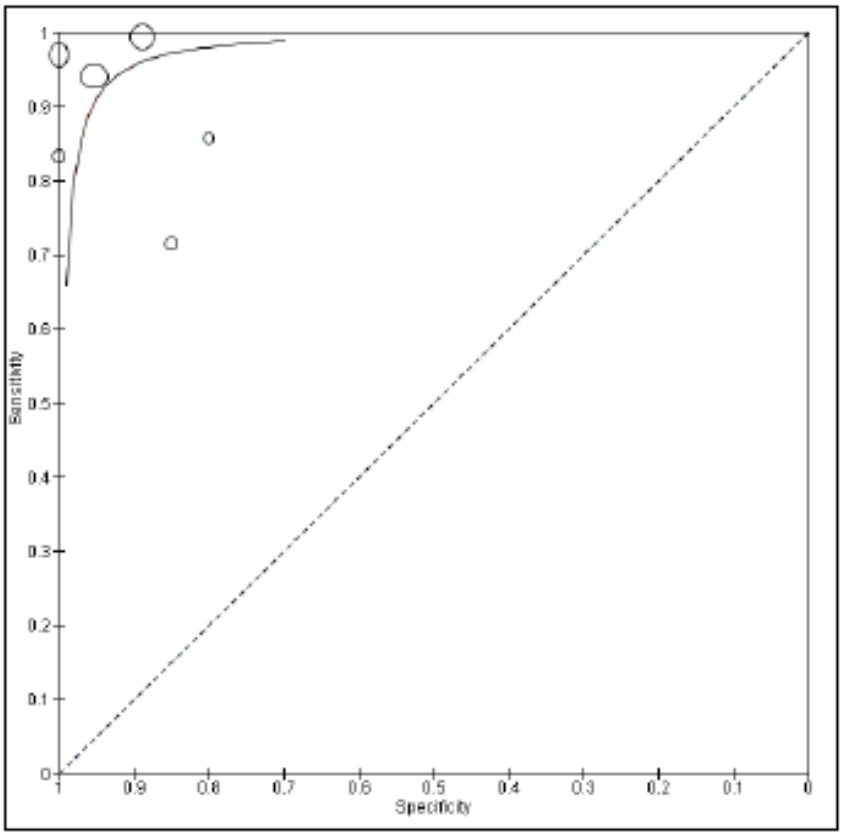
Figure 2: Forest plots for individual studies and pooled estimates of sensitivity and specificity with corresponding heterogeneity statistics of confocal laser endomicroscopy for the diagnosis of oral squamous cell carcinoma



The positive likelihood ratio ranged from 4.28 (95% CI, 0.73–25.06) to 98.5 (95% CI, 6.24–1554.1) and the negative likelihood ratio ranged from 0.008 (95% CI, 0.001–0.055) to 0.3 (95% CI, 0.14–0.78). The pooled positive and negative likelihood ratios were 10.85 (95% CI, 5.4–21.7; I2 = 55.9%) and 0.08 (95% CI, 0.03–0.2; I2 = 83.5%). The diagnostic odds ratio (DOR) ranged from 14.1 (95% CI, 2.61–76.6) to 2861.7 (95% CI, 151.3–54123.7). The pooled DOR was 174.45 (95% CI, 34.51–881.69; I2 = 73.6%).

The form of the HSROC curve in Figure 3 and the area under the curve (AUC) of 0.97 suggested the absence of a threshold effect. The summary ROC curve in Figure 3 describes that effect, which accounts for most of the heterogeneity in these studies. In addition, by using a random-effects method, between-study variation was considered. The shape of the prediction region is meant to give a graphic representation of the extent of between-study heterogeneity, is dependent on the assumption of a bivariate normal distribution for the random effects, and should therefore not be over-interpreted.

Figure 3: HSROC (Hierarchal summary receiver operating characteristic) curve of sensitivity (Y-axis) vs. specificity (X-axis) of CLE for diagnosing OSCC.



Points represent sensitivity and specificity of one study. The size of the points is proportional to the study sample size. The solid line shows the summary ROC curve.

Heterogeneity Analysis

Concerning heterogeneity analysis, a Spearman correlation coefficient of 0.314 (p = 0.544) suggested the lack of a threshold effect. Statistical analysis of the sources of heterogeneity was not performed as subgroups were too small (two or three studies per group).

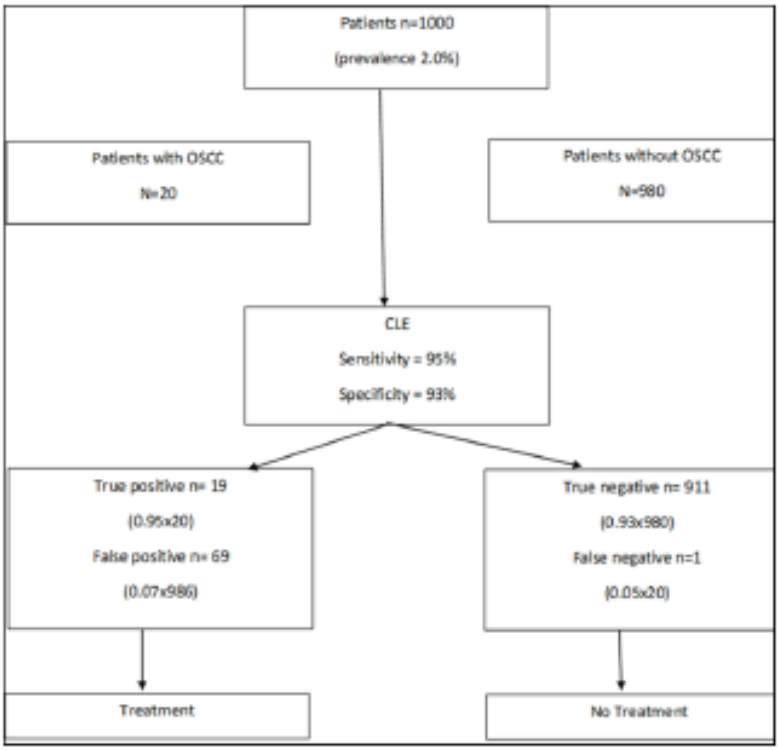
The sources of bias include variation in (i) sites within the oral cavity assessed; (ii) type of CLE device and (iii) level of CLE training of the reviewers.

As per the general methodology rules specified for Cochrane reviews (60), tests for funnel plot asymmetry (to assess publication bias) should be used only when there are at least 10 studies included in the meta-analysis, because when there are fewer studies the power of the tests is too low to distinguish chance from real asymmetry. As six studies have been included in the meta-analysis a funnel plot was not performed.

Based on recent epidemiological data (61), the global prevalence of OSCC is 2%. Using available data together with our results, the absolute number of true and false positives and negatives can be estimated in a hypothetical cohort of 1000 patients. This means that 20 subjects in this cohort would

have OSCC. By using CLE as a diagnostic tool with a sensitivity of 95% and a specificity of 93%, one of these 20 OSCCs would go undetected, while 69 patients would be unnecessarily treated (Figure 4).

Figure 4: The consequences of using CLE for OSCC diagnosis in a cohort of 1000 subjects.



The use of CLE would lead to 88 patients being treated, of which 69 would not need to be treated; 911 patients would not be treated, of which only one would have necessitated treatment.
*Abbreviations: OSCC – Oral Squamous Cell Carcinoma; CLE- Confocal Laser Endomicroscopy.

Discussion

CLE is a novel, non-invasive diagnostic tool that allows real-time cellular imaging of the epithelium till the upper layers of the dermis at resolutions comparable to histology. The confocal criteria for CLE diagnosis of OSCC is easy to learn and even nonexperts in the field of CLE have been able to make a precise diagnosis of OSCC by using this criteria (56). Previous research has indicated the efficient and precise ability of CLE to visualize dysplastic head and neck squamous cell mucosa, with close reproducibility of the histopathological diagnosis (62, 63).

This systematic review and meta-analysis compare the diagnostic accuracy of CLE to histopathological examination from in /ex vivo specimens using the results of 6 studies which included a total number of 361 lesions. The literature search strategy used wide-ranging keywords in multiple databases to find as many studies as possible.

The results of the meta-analysis show a sensitivity of 95% and a specificity of 93% for the CLE diagnosis of OSCC. However, care must be taken while interpreting these high values of both sensitivity and specificity. The substantial heterogeneity indicates the direct assessment of CLE diagnostic accuracy

between the included studies impossible. CLE sensitivity for the diagnosis of OSCC ranged between 71.4% to 99.3%, and its specificity ranged between 80% to 100%. Although statistically insignificant (possibly due to insufficient statistical power), the variations could still be explained by the different confocal criteria and different experimental designs (*in vivo* vs *ex vivo*), but also investigator skill/experience, and probably other indefinite heterogeneity sources. Investigator experience could influence diagnostic accuracy even when using the same diagnostic criteria as it has been demonstrated that there is a clear correlation of interpretation accuracy and the expertise level (57).

Of the six studies included in our review, three are ex vivo (55, 57, 58) in design and three are in-vivo (24, 56, 59) in design. However, on comparing the CLE images for fresh-frozen and formalin-fixed tissue from the same patients, only marginal differences (regarding the range of brightness) in morphology were observed with no variation in the resolution of the images. Thus, stipulating that the images on ex vivo specimens would be largely reproducible in an in-vivo situation (55).

Clinical Relevance

Efficiency and acceptability of this instrument has been addressed by Nathan C et al (24), where they explain the advantage of CLE imaging as it decreases the sampling errors encountered during tissue biopsy or could lead to the decision of avoiding a biopsy altogether and leading to real-time management decisions.

The gold standard treatment for oral dysplastic lesions is excision or laser ablation, and lower grade suspicious lesions are usually kept under observation, due to possible chances of regression (9-45%) (64). But this decision is highly criticised due to higher rates of recurrence, metastasis and incipient malignant progressions, and it is argued that clinical examinations and palpations are insufficient in determining the malignant potential of a visually low suspicious presentation of a lesion (65). Hence, the potential utilization of CLE as a surveillance tool which could aid in diagnosing which lesions can potentially be observed instead of being resected and which lesions demand aggressive management.

The results of this systematic review could have potential implications for patients suffering from OSCC. Based on recent epidemiological data (61), the prevalence of an OSCC in the world is 2%. Using this available data together with our results, the absolute number of true and false positives and negatives can be estimated in a hypothetical cohort of 1000 subjects. This means that 20 subjects in this cohort would have OSCC. By using CLE as a diagnostic tool with a sensitivity of 95% and a specificity of 93%, just one of these 20 OSCC'S would go unnoticed, while 69 patients would be unnecessarily treated (Figure 4).

In vivo CLE could become a very valuable and beneficial instrument in the diagnosis of OSCC; but, in order for it to be regarded as a potential replacement for the gold standard reference of histopathology, this non-invasive technique should have the capacity to distinguish between the different histopathological grades of OSCC (66). Although the treatment strategies for OSCC are largely based on the TNM staging of the tumour (67), the histopathological grade is also of critical importance when strategizing the therapeutic approach to treat an OSCC patient.

Strengths and Limitations

The included studies had some limitations such as the improper visualization of the dorsal surface of the tongue due to the keratinized filiform papillae and the limited accuracy of detection of lesions below the superficial mucosa (24, 55). Most of the included studies had a small sample size and reproducibility of the results are not reliable enough to make concrete diagnosis and treatment decisions (24, 58, 59). Due to ex vivo experiment design, one study is limited by the unavailability of fresh-frozen tissues for all included patients (55) as this limits the transferability of their results to the intraoperative situation due to the different constitution and molecular tissue structure caused by formaldehyde-induced protein and DNA crosslinking and the resulting change of tissue autofluorescence.

One of the included studies; notes that no study so far has investigated whether CLE can be used to visualize the border between cancerous and adjacent healthy tissue, which would be highly beneficial in head and neck cancer surgery (55).

To enable homogeneity, future studies could consider reporting investigator experience, number of examined lesions and/or attended skill development courses. Development and validation of a standardised confocal criteria for OSCC diagnosis via international agreement is desirable. Global consensus is essential for this instrument to begin its journey towards replacing the invasive surgical and histopathological techniques for screening purposes

Future Directions

Regarding the future scope of CLE, transference of the first experimental results of CLE in the human oral cavity into an effective and evidence based clinical setting will be a crucial step.

More studies exploring the diagnostic accuracy of in-vivo confocal microscopy for OSCC are expected in future. To help comparability of the results it is recommended that the histopathological examination of the excisional biopsy specimen be utilized as a reference standard.

Conclusions

Confocal Laser Endomicroscopy is a promising technique in the diagnosis of Oral Squamous Cell Carcinoma. A definitive conclusion could only be drawn when a higher number of studies, possibly with homogeneous methodological approach, will be available.

Author Contributions

S.S., X.J. and L.J. contributed to the conception of this study and performed the preliminary documentation. All authors participated in the design of the study and implemented the research. S.S, X.J., L.J. and R.L. were responsible for the data acquisition, selection and analysis, and clinical interpretation of the data. S.S., X.J., L.J., R.L., P.S. and R.M. participated in the statistical analysis and contributed to the interpretation of the results as well as the manuscript drafting and writing of the study. S.S., R.L., P.S., R.M., L.J. have revised critically the manuscript for important intellectual content. All authors reviewed and approved the final manuscript.

Conflicts of Interest

The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

References

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA: a cancer journal for clinicians. 2015;65(2):87-108.
2. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. International journal of cancer. 2010;127(12):2893-917.
3. Forastiere A, Koch W, Trotti A, Sidransky D. Head and neck cancer. The New England journal of medicine. 2001;345(26):1890-900.
4. Marur S, Forastiere AA. Head and neck cancer: changing epidemiology, diagnosis, and treatment. Mayo Clinic proceedings. 2008;83(4):489-501.
5. Jadhav KB, Gupta N. Clinicopathological prognostic implicators of oral squamous cell carcinoma: need to understand and revise. N Am J Med Sci. 2013;5(12):671-9.
6. Sciubba JJ, Larian B. Oral squamous cell carcinoma: early detection and improved 5-year survival in 102 patients. General dentistry. 2018;66(6):e11-e6.
7. Mehrotra R, Yadav S. Oral squamous cell carcinoma: etiology, pathogenesis and prognostic value of genomic alterations. Indian journal of cancer. 2006;43(2):60-6.
8. Mohan M, Jagannathan N. Oral field cancerization: an update on current concepts. Oncol Rev. 2014;8(1):244-.

9. Slaughter DP, Southwick HW, Smejkal W. Field cancerization in oral stratified squamous epithelium; clinical implications of multicentric origin. Cancer. 1953;6(5):963-8.

10. Yardimci G, Kutlubay Z, Engin B, Tuzun Y. Precancerous lesions of oral mucosa. World J Clin Cases. 2014;2(12):866-72.

11. Warnakulasuriya S, Ariyawardana A. Malignant transformation of oral leukoplakia: a systematic review of observational studies. Journal of oral pathology & medicine : official publication of the International Association of Oral Pathologists and the American Academy of Oral Pathology. 2016;45(3):155-66.

12. Reichart PA, Philipsen HP. Oral erythroplakia--a review. Oral oncology. 2005;41(6):551-61.

13. Chiesa F, Mauri S, Tradati N, Calabrese L, Giugliano G, Ansarin M, et al. Surfing prognostic factors in head and neck cancer at the millennium. Oral oncology. 1999;35(6):590-6.

14. Hinni ML, Ferlito A, Brandwein-Gensler MS, Takes RP, Silver CE, Westra WH, et al. Surgical margins in head and neck cancer: a contemporary review. Head & neck. 2013;35(9):1362-70.

15. Cikojević D, Gluncić I, Pesutić-Pisac V. Comparison of contact endoscopy and frozen section histopathology in the intra-operative diagnosis of laryngeal pathology. The Journal of laryngology and otology. 2008;122(8):836-9.

16. Miyawaki A, Hijioka H, Ishida T, Nozoe E, Nakamura N, Oya R. Intraoperative frozen section histological analysis of resection samples is useful for the control of primary lesions in patients with oral squamous cell carcinoma. Molecular and clinical oncology. 2015;3(1):55-62.

17. Ravi SB, Annavajjula S. Surgical margins and its evaluation in oral cancer: a review. J Clin Diagn Res. 2014;8(9):ZE01-ZE5.

18. Barroso EM, Aaboubout Y, van der Sar LC, Mast H, Sewnaik A, Hardillo JA, et al. Performance of Intraoperative Assessment of Resection Margins in Oral Cancer Surgery: A Review of Literature. Front Oncol. 2021;11:628297.

19. Guida A, Maglione M, Crispo A, Perri F, Villano S, Pavone E, et al. Oral lichen planus and other confounding factors in narrow band imaging (NBI) during routine inspection of oral cavity for early detection of oral squamous cell carcinoma: a retrospective pilot study. BMC Oral Health. 2019;19(1):70-.

20. Vu AN, Matias M, Farah CS. Diagnostic accuracy of Narrow Band Imaging for the detection of oral potentially malignant disorders. Oral diseases. 2015;21(4):519-29.

21. Luo X, Xu H, He M, Han Q, Wang H, Sun C, et al. Accuracy of autofluorescence in diagnosing oral squamous cell carcinoma and oral potentially malignant disorders: a comparative study with aero-digestive lesions. Scientific reports. 2016;6(1):29943.

22. Bagri-Manjrekar K, Chaudhary M, Sridharan G, Tekade S, Gadbail A, Khot K. In vivo autofluorescence of oral squamous cell carcinoma correlated to cell proliferation rate. Journal of Cancer Research and Therapeutics. 2018;14(3):553-8.

23. Pałasz P, Adamski Ł, Górska-Chrząstek M, Starzyńska A, Studniarek M. Contemporary Diagnostic Imaging of Oral Squamous Cell Carcinoma - A Review of Literature. Pol J Radiol. 2017;82:193-202.

24. Nathan CA, Kaskas NM, Ma X, Chaudhery S, Lian T, Moore-Medlin T, et al. Confocal Laser Endomicroscopy in the Detection of Head and Neck Precancerous Lesions. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. 2014;151(1):73-80.

25. Martirosyan NL, Eschbacher JM, Kalani MY, Turner JD, Belykh E, Spetzler RF, et al. Prospective evaluation of the utility of intraoperative confocal laser endomicroscopy in patients with brain neoplasms using fluorescein sodium: experience with 74 cases. Neurosurgical focus. 2016;40(3):E11.

26. Wallace MB, Sharma P, Lightdale C, Wolfsen H, Coron E, Buchner A, et al. Preliminary accuracy and interobserver agreement for the detection of intraepithelial neoplasia in Barrett's esophagus with probe-based confocal laser endomicroscopy. Gastrointestinal endoscopy. 2010;72(1):19-24.

27. De Palma GD. Confocal laser endomicroscopy in the "in vivo" histological diagnosis of the gastrointestinal tract. World journal of gastroenterology. 2009;15(46):5770-5.

28. Kiesslich R, Burg J, Vieth M, Gnaendiger J, Enders M, Delaney P, et al. Confocal laser endoscopy for diagnosing intraepithelial neoplasias and colorectal cancer in vivo. Gastroenterology. 2004;127(3):706-13.

29. Goetz M. Colonoscopic Surveillance in Inflammatory Bowel Disease: State of the Art Reduction of Biopsies. Digestive Diseases. 2011;29(suppl 1)(Suppl. 1):36-40.

30. Tan J, Quinn MA, Pyman JM, Delaney PM, McLaren WJ. Detection of cervical intraepithelial neoplasia in vivo using confocal endomicroscopy. BJOG : an international journal of obstetrics and gynaecology. 2009;116(12):1663-70.

31. Carlson K, Pavlova I, Collier T, Descour M, Follen M, Richards-Kortum R. Confocal microscopy: imaging cervical precancerous lesions. Gynecol Oncol. 2005;99(3 Suppl 1):S84-8.

32. Pierre ML, Stephen L, Annette M, Jean CLR, Marshall A, Calum EM. Confocal fluorescence microendoscopy of bronchial epithelium. Journal of biomedical optics. 2009;14(2):1-10.

33. Thiberville L, Moreno-Swirc S, Vercauteren T, Peltier E, Cavé C, Bourg Heckly G. In vivo imaging of the bronchial wall microstructure using fibered confocal fluorescence microscopy. American journal of respiratory and critical care medicine. 2007;175(1):22-31.

34. Fuchs FS, Zirlik S, Hildner K, Schubert J, Vieth M, Neurath MF. Confocal laser endomicroscopy for diagnosing lung cancer in vivo. The European respiratory journal. 2013;41(6):1401-8.

35. Sonn GA, Jones SN, Tarin TV, Du CB, Mach KE, Jensen KC, et al. Optical biopsy of human bladder neoplasia with in vivo confocal laser endomicroscopy. The Journal of urology. 2009;182(4):1299-305.

36. Chang TC, Liu J-J, Liao JC. Probe-based confocal laser endomicroscopy of the urinary tract: the technique. J Vis Exp. 2013(71):e4409-e.

37. Snuderl M, Wirth D, Sheth SA, Bourne SK, Kwon CS, Ancukiewicz M, et al. Dye-enhanced multimodal confocal imaging as a novel approach to intraoperative diagnosis of brain tumors. Brain pathology (Zurich, Switzerland). 2013;23(1):73-81.

38. Charalampaki P, Javed M, Daali S, Heiroth HJ, Igressa A, Weber F. Confocal Laser Endomicroscopy for Real-time Histomorphological Diagnosis: Our Clinical Experience With 150 Brain and Spinal Tumor Cases. Neurosurgery. 2015;62 Suppl 1:171-6.

39. Fujita Y, Wei L, Cimino PJ, Liu JTC, Sanai N. Video-Mosaicked Handheld Dual-Axis Confocal Microscopy of Gliomas: An ex vivo Feasibility Study in Humans. Front Oncol. 2020;10:1674.

40. White WM, Rajadhyaksha M, González S, Fabian RL, Anderson RR. Noninvasive imaging of human oral mucosa in vivo by confocal reflectance microscopy. The Laryngoscope. 1999;109(10):1709-17.

41. Clark AL, Gillenwater AM, Collier TG, Alizadeh-Naderi R, El-Naggar AK, Richards-Kortum RR. Confocal microscopy for real-time detection of oral cavity neoplasia. Clinical cancer research : an official journal of the American Association for Cancer Research. 2003;9(13):4714-21.

42. Just T, Stave J, Boltze C, Wree A, Kramp B, Guthoff RF, et al. Laser scanning microscopy of the human larynx mucosa: a preliminary, ex vivo study. The Laryngoscope. 2006;116(7):1136-41.

43. Abbaci M, Temam S, Casiraghi O, Vielh P, Bosq J, Fouret P, et al. Characterization of laryngeal carcinoma by confocal endomicroscopy. Head & Neck Oncology. 2009;1(1):O14.

44. Muldoon TJ, Roblyer D, Williams MD, Stepanek VM, Richards-Kortum R, Gillenwater AM. Noninvasive imaging of oral neoplasia with a high-resolution fiber-optic microendoscope. Head & neck. 2012;34(3):305-12.

45. Farahati B, Stachs O, Prall F, Stave J, Guthoff R, Pau HW, et al. Rigid confocal endoscopy for in vivo imaging of experimental oral squamous intra-epithelial lesions. Journal of oral pathology & medicine : official publication of the International Association of Oral Pathologists and the American Academy of Oral Pathology. 2010;39(4):318-27.

46. Zheng W, Harris M, Kho KW, Thong PS, Hibbs A, Olivo M, et al. Confocal endomicroscopic imaging of normal and neoplastic human tongue tissue using ALA-induced-PPIX fluorescence: a preliminary study. Oncology reports. 2004;12(2):397-401.

47. Thong PS, Olivo M, Kho KW, Zheng W, Mancer K, Harris M, et al. Laser confocal endomicroscopy as a novel technique for fluorescence diagnostic imaging of the oral cavity. Journal of biomedical optics. 2007;12(1):014007.

48. Maitland KC, Gillenwater AM, Williams MD, El-Naggar AK, Descour MR, Richards-Kortum RR. In vivo imaging of oral neoplasia using a miniaturized fiber optic confocal reflectance microscope. Oral oncology. 2008;44(11):1059-66.

49. Haxel BR, Goetz M, Kiesslich R, Gosepath J. Confocal endomicroscopy: a novel application for imaging of oral and oropharyngeal mucosa in human. European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery. 2010;267(3):443-8.

50. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ (Clinical research ed). 2009;339:b2535.

51. McGrath TA, Alabousi M, Skidmore B, Korevaar DA, Bossuyt PMM, Moher D, et al. Recommendations for reporting of systematic reviews and meta-analyses of diagnostic test accuracy: a systematic review. Systematic reviews. 2017;6(1):194.

52. Schardt C, Adams MB, Owens T, Keitz S, Fontelo P. Utilization of the PICO framework to improve searching PubMed for clinical questions. BMC Medical Informatics and Decision Making. 2007;7(1):16.

53. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Annals of internal medicine. 2011;155(8):529-36.

54. Leeflang MMG, Deeks JJ, Takwoingi Y, Macaskill P. Cochrane diagnostic test accuracy reviews. Systematic reviews. 2013;2:82-.

55. Linxweiler M, Kadah BA, Bozzato A, Bozzato V, Hasenfus A, Kim YJ, et al. Noninvasive histological imaging of head and neck squamous cell carcinomas using confocal laser endomicroscopy. European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery. 2016;273(12):4473-83.

56. Oetter N, Knipfer C, Rohde M, Wilmowsky C, Maier A, Brunner K, et al. Development and validation of a classification and scoring system for the diagnosis of oral squamous cell carcinomas through confocal laser endomicroscopy. Journal of translational medicine. 2016;14(1).

57. Shavlokhova V, Flechtenmacher C, Sandhu S, Pilz M, Vollmer M, Hoffmann J, et al. Detection of oral squamous cell carcinoma with ex vivo fluorescence confocal microscopy: Sensitivity and specificity compared to histopathology. Journal of biophotonics. 2020;13(9).

58. Shinohara S, Funabiki K, Kikuchi M, Takebayashi S, Hamaguchi K, Hara S, et al. Real-time imaging of head and neck squamous cell carcinomas using confocal micro-endoscopy and applicable dye: A preliminary study. Auris, nasus, larynx. 2020;47(4):668-75.

59. Dittberner A, Ziadat R, Hoffmann F, Pertzborn D, Gassler N, Guntinas-Lichius O. Fluorescein-Guided Panendoscopy for Head and Neck Cancer Using Handheld Probe-Based Confocal Laser Endomicroscopy: A Pilot Study. FRONTIERS IN ONCOLOGY. 2021;11.

60. Debray TPA, Moons KGM, Riley RD. Detecting small-study effects and funnel plot asymmetry in meta-analysis of survival data: A comparison of new and existing tests. Res Synth Methods. 2018;9(1):41-50.

61. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a cancer journal for clinicians. 2018;68(6):394-424.

62. Pogorzelski B, Hanenkamp U, Goetz M, Kiesslich R, Gosepath J. Systematic intraoperative application of confocal endomicroscopy for early detection and resection of squamous cell carcinoma of the head and neck: a preliminary report. Archives of otolaryngology--head & neck surgery. 2012;138(4):404-11.

63. Just T, Pau HW. Intra-operative application of confocal endomicroscopy using a rigid endoscope. The Journal of laryngology and otology. 2013;127(6):599-604.

64. Lumerman H, Freedman P, Kerpel S. Oral epithelial dysplasia and the development of invasive squamous cell carcinoma. Oral surgery, oral medicine, oral pathology, oral radiology, and endodontics. 1995;79(3):321-9.

65. Arnaoutakis D, Bishop J, Westra W, Califano JA. Recurrence patterns and management of oral cavity premalignant lesions. Oral oncology. 2013;49(8):814-7.

66. Akhter M, Hossain S, Rahman QB, Molla MR. A study on histological grading of oral squamous cell carcinoma and its co-relationship with regional metastasis. Journal of oral and maxillofacial pathology : JOMFP. 2011;15(2):168-76.

67. Almangush A, Mäkitie AA, Triantafyllou A, de Bree R, Strojan P, Rinaldo A, et al. Staging and grading of oral squamous cell carcinoma: An update. Oral oncology. 2020;107:104799.

End of Paper

SECTION G: USING THE EVIDENCE

Overview of Section G

This section provides a brief discussion and conclusion to the thesis along with an outline of the strengths and limitations of this project. It also provides an insight to the future and next phases of this project.

11

RESEARCH UPDATE

11.1 PREFACE

This Chapter brings together the evidence obtained throughout this PhD research. Section 11.2 provides an overview and recap of the research background, along with the specified objectives. Section 11.3 covers the key findings and an overview of the key discussion points in five sub-sections (11.3.1–11.3.5). The overall significance of the research is described in Section 10.4, followed by issues related to the findings in Section 10.5.

11.2 OVERVIEW OF THE RESEARCH

This research has explored quantitative and qualitative aspects of HPV infection and cancers amongst Indigenous populations; both at a global and an Australian level. The overall research aimed to better understand risk factors associated with oral HPV infections and to explore the views and experiences of Indigenous populations of HPV infection and its associated cancers. This research has 4 main aims which has been scoped around four objectives covered in seven chapter (as mentioned in Chapter 3) and shown in Table 11.1.

Table 11.1: Scope of thesis according to aims of project

	Research Aims	Chapters
1	Analyse and correlate socio-demographic variables, oral health behaviours and sexual behaviours with the presence of oral HPV infection and its subtypes.	Chapter 5, 7 Appendix D
2	Evaluate risk factors associated with incidence, persistence and clearance of HPV infection at 12 months follow up	Chapter 6
3	Evaluate the qualitative experiences of Indigenous populations at a global level regarding HPV infections, vaccines and cancers	Chapter 8, 9 Appendix E
4	Evaluate the diagnostic accuracy of a novel, non-invasive and portable instrument for screening oropharyngeal carcinoma	Chapter 10

11.3 PROGRESS OF RESEARCH

The HPV-OPC project has completed baseline and 12-month follow up, with 24-month follow-up ongoing. Each visit included the collection of a saliva sample for HPV DNA detection, and a questionnaire.

11.3.1 Baseline

The data collected at baseline (Appendix A) contained information on sociodemographic characteristics, health-related behaviours including tobacco and alcohol use, sexual history, experiences of racism and cultural identity. Health state preferences, utilities on oral HPV infection, HPV vaccination and oropharyngeal squamous cell carcinoma were also collected. The fact that over 1000 participants were recruited in less than 12 months demonstrates the widespread community support of the study aims and objectives.

The baseline findings have been published (Appendix D), and demonstrate higher prevalence of oral HPV infection in comparison with general population estimates. There was an especially high prevalence of HPV 13 and 32; the HPV types associated with Heck's Disease.

11.3.2 *12-month follow-up*

The data collected at the 12-month follow-up (Appendix B) contained information on health-related behaviours such as tobacco and alcohol use, physical activity, experiences of pain, recent life events and self-rated oral and general health. Health state preferences and utilities on HPV carriage, HPV vaccination and cervical cancer were collected among women only. Findings from the 12-month are both published (Appendix F) and submitted for publication (Chapter 6).

A retention of 78% was achieved, with follow-up prematurely suspended due to COVID-19 restrictions. The prevalence of any oral HPV infection increased from 34% at baseline to 44% at 12-month follow-up. An increase in HPV types 13 or 32 (20% at baseline and 34% at 12-month follow-up) was observed. Factors associated with persistence and clearance of oral HPV infections included location of residence and unsafe oral sexual behaviours.

11.3.3 24-month follow-up

The 24-month follow-up is currently underway. Data contains information on health-related behaviours such as tobacco and alcohol use, physical activity, experience of pain, recent life events, sleep and self-rated oral and general health. COVID-19 restrictions have again posed barriers to completion, but the excellent working relationship of our senior Indigenous Research Officer (Joanne Hedges), with Aboriginal Health Care Councils and other stakeholders has mitigated this.

11.4 INTERNATIONAL PAPILLOMAVIRUS SOCIETY STATEMENT FOR INDIGENOUS POPULATIONS

The WHO (World Health organisation) in September, 2018 declared HPV infection and its associated cancers as a public health concern. It stated that the infection is preventable and treatable, with a call for action from all representative bodies issued. The principles of equity were emphasised, which is fundamental to all countries currently developing strategies to eliminate cervical cancer as a public health problem.[1]

The International Papillomavirus Society (IPVS) is a global organization that supports best practice and evidence-based research, strategies, and policies to prevent HPV-related diseases worldwide. In response to the WHO declaration, the IPVS issued a statement in support of the action.[2] Within the statement contained a section prioritising equitable strategies as ‘Equity in cervical cancer prevention for all women’. This statement recognised the unequal burden from cervical cancer and other HPV-related diseases that Indigenous peoples face in many areas of the world. It recognised the importance of culturally appropriate best practices in research and policy to reduce this burden of disease.

The IPVS statement describes an approach to achieve equitable health outcomes for Indigenous peoples[2];

"Strategies are required that consider co-creation of methods and tools, that acknowledge the importance of shared data ownership, and include Indigenous "ways of being, doing, and knowing", i.e., Indigenous beliefs, practices and knowledge systems; and determinants of 'responsibility', 'relationships' and 'respect'. Indigenous leadership is key to developing prioritisation of research focus and methods leading to solutions that are acceptable, appropriate and sustainable, incorporating the WHO health rights platform and best practice principles."

The following acknowledgements were issued to address the public health concern amongst global Indigenous populations:

- Acknowledge the fundamental right of Indigenous peoples to equal protection against, and treatment of, HPV-related diseases consistent with the United Nations Declaration on the Rights of Indigenous Peoples
- Develop meaningful respectful partnerships with Indigenous researchers, leaders and communities to conduct work addressing data quality, policy, program and research development in relation to HPV-related disease and HPV Indigenous workforce capacity development;
- Ensure that HPV related issues affecting Indigenous people are presented at relevant forums.

These guidelines were deeply embedded in the HPV-OPC project. The project design, recruitment and governance were orchestrated through the study's Indigenous Reference Group, through the Aboriginal Community Controlled Health Organisations (ACCHO) stakeholder groups and by the Senior Aboriginal research officer (Joanne Hedges). The

execution of this project in accordance with the international guidelines from the IPVS and WHO are important indicators of the ethical and cultural considerations, as well as the project's global relevance.

11.5 REFERENCES:

1. https://www.who.int/reproductivehealth/cervical-cancer-public-health-concern/en/ (accessed September, 2021)
2. Lawton B, Heffernan M, Wurtak G, et al. IPVS Policy Statement addressing the burden of HPV disease for Indigenous peoples. *Papillomavirus Res*. 2020;9:100191. doi:10.1016/j.pvr.2019.100191

12

Conclusion and Recommendations

12.1 **CONCLUSION**

The work presented in this thesis provides evidence that Indigenous populations show a higher prevalence of HPV infections and associated carcinomas. There is lack of awareness about the association of HPV infections and cancer.

The work carried out as a part of this thesis and the HPV-OPC study was overseen by an established Indigenous Reference group, who were also key stakeholders in the study. This association was essential in developing a strong rapport with the South Australian communities and Aboriginal Health Organisations. The most significant attribute of this study was the strong buy-in by all the participants and partnering communities.

The most prevalent HPV types found was HPV 13 and 32. Although HPV 13 and 32 associations with cancers are benign, the exceptionally high carriage among the Indigenous Australian adult requires more research. The prevalence of the high-risk HPV types (16 and 18) was higher than previously reported non-Indigenous Australian and international population level estimates. To the best of our knowledge, this is the first study to report the incidence, persistence and clearance of oral HPV infections among Indigenous Australians.

The qualitative aspect of this thesis provided a clearer understanding of Indigenous experiences, barriers, facilitators of HPV infections and cancers. The psycho-oncological approach to understanding the perception of cancer amongst Indigenous families provides valuable information regarding the involvement of families in cancer care.

The concluding Chapter describes a range of diagnostic and screening possibilities for future clinical examination phases of the HPV-OPC study. The most important barrier amongst Indigenous population groups is the lack of accessibility of medical services and remote locations of residence. Confocal laser endomicroscope is a promising tool which could potentially be used in field for large, remote oral cancer screening programs.

12.2 SPECIFIC RECOMMENDATIONS FROM THIS RESEARCH

The findings of this study indicate that Indigenous Australians may be at higher risk of developing HPV-related oral cancer, which suggests that increased HPV vaccination coverage among this vulnerable population may be beneficial.

The increased risk of developing oropharyngeal cancer means that frequent clinical examinations, culturally-safe follow-up protocols and screening for oral and oropharyngeal cancer are required. Earlier detection can lead to a better prognosis and improve quality of life post treatment.

The study was able to identify risk factors associated with OPSCC-related HPV types (HPV 16 or 18) among Indigenous Australians, and in future may help to examine development of early stage OPSCC. This recognition could lead to earlier referrals for treatment and contribute to refining HPV infection-related health state appraisals among Indigenous Australians. This information, in partnership with the South Australian Indigenous community, will significantly assist policymakers, ACCHOs and health service providers to regulate the influence of oral HPV infections on OPSCCs, and the utility, acceptance and cost-effectiveness of extending publicly-funded HPV vaccination among Indigenous groups.

12.3 LIMITATIONS AND STRENGTHS

12.3.1 Limitations

Clinical examinations were a crucial part of this research, but this step had to be postponed due to COVID-19 restrictions. Our clinical results are solely based on DNA testing of three consecutive saliva samples collected from participants. Clinical examinations are essential to determine the presence of premalignant or malignant lesions among the participants carrying high risk HPV types and also focal or multifocal epithelial hyperplastic lesions amongst the participants carrying HPV 13 and 32. Another limitation was the over-representation of women

and participants residing in remote areas, meaning our findings are not representative and therefore not generalisable

12.3.2 Strengths

The main strength of this study lies in the strong community support and participant buy-in from recruiting through to 24-month follow-up. The Indigenous Reference group provided oversight and cultural guidance on all aspects of recruitment strategies and data collection. This is one of the largest cohorts of Indigenous populations to have been established in Australia and, indeed, the world. Although COVID-19 led to removal of the clinical componentof the thesis, it resulted in the addition of a qualitative component. This added further richnessto the research conducted in this thesis. The qualitative components have helped facilitate better understanding of HPV infections and barriers to HPV vaccine uptake from an Indigenous perspective.

13

Appendices

13.1 Appendix A: Baseline questionnaire for the HPV-OPC Study

THE UNIVERSITY of ADELAIDE

AUSTRALIAN RESEARCH CENTRE FOR POPULATION ORAL HEALTH
SCHOOL OF DENTISTRY

HPV and OROPHARYNGEAL CANCER (THROAT CANCER) STUDY

BASELINE QUESTIONNAIRE-(Section D-P)

1. Participant ID Number_____
2. Interviewer name_____
3. Date of interview (dd/mm/yy)_____
4. Date of birth (dd/mm/yy)_____
5. Sex: Male/Female/Other _____

Please answer ALL of the sections in the survey, even if they do not seem to be directly relevant to *you*. Everything you tell us will be treated in strict confidence but you are free to leave any specific questions that you do not wish to answer.

If you are not sure of the correct answer, please give us your best estimate. We are asking many different people the same sets of questions and we are very interested in the different types of responses.

D. THESE QUESTIONS ARE ABOUT YOUR BACKGROUND. THERE ARE NO RIGHT OR WRONG ANSWERS				
D1. Do you identify as being?	Aboriginal ☐1	Torres Strait Islander ☐2	Both ☐3	Other ☐4

D2. Level of education	No schooling ☐1	Primary school ☐2	High school ☐3	Trade or TAFE ☐4	University ☐5

D3. Income	Job ☐1	Centrelink payment ☐2	Other_____ ☐3

D4. Health Care Card	Yes ☐1	No ☐2	Don't know ☐3

D5. How many people stayed in the house last night?	Write the number in this box

D6. Do you own a car?	Yes ☐1	No ☐2	Don't know ☐3
D7. Do you borrow a car?	Yes ☐1	No ☐2	Don't know ☐3

E. THESE QUESTIONS ARE ABOUT YOUR ALCOHOL AND TOBACCO CONSUMPTION			
If you have never smoked or have smoked fewer than 100 cigarettes in your lifetime go to question E7.			
E1. Have you smoked more than 100 cigarettes in your lifetime?	Yes ☐1	No ☐2 (If no please go to question E7)	Rather not say ☐3
*If you **currently** smoke cigarettes please answer Q E2-Q E3*			
E2. For how long have you smoked cigarettes?	Years	Months	
E3. On a usual day how many cigarettes do you smoke?	Write the number in this box		
*If you are a **former** smoker please answer Q E4 –Q E6*			
E4. How long ago did you stop smoking cigarettes?	Years	Months	

E5. For how long had you smoked cigarettes?	☐ Years	☐ Months	
E6. On a usual day, how many cigarettes did you smoke?	☐ Write the number in this box		
E7. Do you chew tobacco/ pituri?	Yes ☐1	No ☐2	Rather not say ☐3
If you have never had alcohol in your lifetime please go to question E10			
E8. How often do you drink alcohol?	Daily ☐1	Weekly ☐2	Monthly ☐3	Never ☐4
E9. How much alcohol do you drink per week?	20+ Alcoholic drinks ☐1	8–19 Alcoholic drinks ☐2	1–7 Alcoholic drinks ☐3	No-alcoholic drinks ☐4
E10. Which of the following best describes your non-tobacco substance smoking status eg Vape/e-cigarette?	I currently smoke non-tobacco substances ☐1	I don't smoke non-tobacco substances now but I used to ☐2	I have never smoked non-tobacco substances ☐3
E11. Which of the following best describes your recreational drug use? eg marijuana	I currently use recreational drugs ☐1	I don't use recreational drugs now but I used to ☐2	I have never used recreational drugs ☐3

F. THESE QUESTIONS ARE ABOUT YOUR HUMAN PAPILLOMA VIRUS (HPV) STATUS. HPV IS A VERY COMMON SEXUALLY TRANSMITTED INFECTION THAT MOST AUSTRALIANS EXPERIENCE AT SOME TIME IN THEIR LIVES.

F1. Have you ever been diagnosed with having HPV?	Yes ☐1	No ☐2	Don't know ☐3
F2. Have you ever received a vaccination for HPV?	Yes ☐1	No ☐2	Don't know ☐3
F2a. If yes to F2, how many injections for the HPV vaccination did you receive? (the full amount is 3).	☐ Write the number in this box		
F3. Have you ever had your tonsils taken out?	Yes ☐1	No ☐2	Don't know ☐3
F3a. If yes to F3, what was the age that you had your tonsils taken out?	☐ Write the number in this box		

E5. For how long had you smoked cigarettes?	☐ Years	☐ Months		
E6. On a usual day, how many cigarettes did you smoke?	☐ Write the number in this box			
E7. Do you chew tobacco/ pituri?	Yes ☐1	No ☐2	Rather not say ☐3	
If you have never had alcohol in your lifetime please go to question E10				
E8. How often do you drink alcohol?	Daily ☐1	Weekly ☐2	Monthly ☐3	Never ☐4
E9. How much alcohol do you drink per week?	20+ Alcoholic drinks ☐1	8–19 Alcoholic drinks ☐2	1–7 Alcoholic drinks ☐3	No-alcoholic drinks ☐4
E10. Which of the following best describes your non-tobacco substance smoking status eg Vape/e-cigarette?	I currently smoke non-tobacco substances ☐1	I don't smoke non-tobacco substances now but I used to ☐2	I have never smoked non-tobacco substances ☐3	
E11. Which of the following best describes your recreational drug use? eg marijuana	I currently use recreational drugs ☐1	I don't use recreational drugs now but I used to ☐2	I have never used recreational drugs ☐3	

F. THESE QUESTIONS ARE ABOUT YOUR HUMAN PAPILLOMA VIRUS (HPV) STATUS. HPV IS A VERY COMMON SEXUALLY TRANSMITTED INFECTION THAT MOST AUSTRALIANS EXPERIENCE AT SOME TIME IN THEIR LIVES.

F1. Have you ever been diagnosed with having HPV?	Yes ☐1	No ☐2	Don't know ☐3
F2. Have you ever received a vaccination for HPV?	Yes ☐1	No ☐2	Don't know ☐3

F2a. If yes to F2, how many injections for the HPV vaccination did you receive? (the full amount is 3).	☐ Write the number in this box		
F3. Have you ever had your tonsils taken out?	Yes ☐1	No ☐2	Don't know ☐3
F3a. If yes to F3, what was the age that you had your tonsils taken out?	☐ Write the number in this box		

G. SEXUAL HEALTH BEHAVIOURS; The next section includes private questions about your personal life. These questions are important to understand possible links between life style and oral infections, including HPV.

G1. Altogether, in your life so far, how many people have you kissed passionately on the mouth? ('Passionate kissing' refers to open-mouthed kissing)	None ☐1	1 ☐2	2 to 3 ☐3	4 to 7 ☐4	8 to 15 ☐5	16 to 28 ☐6	29 or more ☐7
G2. Have you ever given oral sex? ('Oral sex' refers to a man's or woman's mouth on a partner's genital area)	No (go to G6) ☐1						Yes (go to next question) ☐2
G3.a How old were you when you first gave oral sex?	<16yrs (go to G4) ☐1						=/ >16yrs (go to G3b) ☐2
G3.b How old? (if =/> 16yrs)	☐☐ Years						
G4. Altogether, in your life so far, how many people have you given oral sex to?	None ☐1	1 ☐2	2 to 3 ☐3	4 to 7 ☐4	8 to 15 ☐5	16 to 28 ☐6	29 or more ☐7
G5. When you give oral sex, how often is a condom or dental dam used? ('Dental dam' refers to a thin square piece of latex used for protection during oral-vaginal or oral-anal sex)	Never ☐1	Seldom ☐2	Occasionally ☐3	Frequently ☐4	Very frequently ☐5	Always ☐6	
G6. Have you ever received oral sex?	No (go to G10) ☐1						Yes (go to next question) ☐2
G7.a How old were you when you first received oral sex?	<16yrs (go to G8) ☐1						=/ >16yrs (go to G7b) ☐2
G7.b How old? (if =/ > 16yrs)	☐☐ Years						
G8. Altogether, in your life so far, how many people have you received oral sex from?	None ☐1	1 ☐2	2 to 3 ☐3	4 to 7 ☐4	8 to 15 ☐5	16 to 28 ☐6	29 or more ☐7

G9. When you receive oral sex, how often is a condom or dental dam used? ('Dental dam' refers to a thin square piece of latex used for protection during oral-vaginal or oral-anal sex)	Never ☐1	Seldom ☐2	Occasionally ☐3	Frequently ☐4	Very frequently ☐5	Always ☐6

G10. Have you ever had sexual intercourse with another person? ('Sexual intercourse' refers to vaginal intercourse and anal intercourse only. 'Sexual intercourse' does not refer to oral sex)	No (go to G13) ☐1	Yes (go to next question) ☐2
G11.a How old were you when you first had sexual intercourse?	<16yrs (go to G12) ☐1	=/ >16yrs (go to G11b) ☐2
G11.b How old? (if =/ > 16yrs)	☐☐ Years	

G12. Altogether, <u>in your life so far</u>, how many people have you had sexual intercourse with?	None ☐1	1 ☐2	2 to 3 ☐3	4 to 7 ☐4	8 to 15 ☐5	16 to 28 ☐6	29 or more ☐7

G13. <u>In your lifetime</u>, who have you had sexual contact with?	Men only ☐1	Mostly men, sometimes women ☐2	Equally men and women ☐3	Women only ☐4	Mostly women, sometimes men ☐5
G14. How would you describe your current relationship status?	Currently in stable, long-term relationship ☐1	Currently in short-term relationships ☐2	Currently single ☐3		

H. SELF-RATED HEALTH

H1. Would you rate your general health as:	Excellent ☐1	Very good ☐2	Good ☐3	Fair ☐4	Poor ☐5
H2. Would you rate your oral health as:	Excellent ☐1	Very good ☐2	Good ☐3	Fair ☐4	Poor ☐5

I. DENTAL BEHAVIOURS

I1. When did you last see a dentist:	Less than one year ago ☐1	More than one year ago ☐2
I2. What is your usual reason for seeing a dentist:	Problem ☐1	Check-up ☐2

I3. During the last year, have you not gone to the dentist because of cost:	Yes ☐1		No ☐2		
I4. How hard would it be for you to pay a $100 dental bill:	Not hard at all ☐1	Not very hard ☐2	A little bit hard ☐1	Very hard ☐2	Could not pay ☐2

J. THE QUESTIONS BELOW ASK ABOUT TROUBLES THAT PEOPLE MAY HAVE IN DAILY LIFE BECAUSE OF DENTAL PROBLEMS.					
How often during the last year….	**Please tick ONE box that best describes your experience**				
J1. … have you had trouble **pronouncing (or saying)** any **words** because of problems with your teeth, mouth or false teeth?	Very often ☐1	Fairly often ☐2	Occasionally ☐3	Hardly ever ☐4	Never ☐5
J2. … have you felt that your **sense of taste** has worsened because of problems with your teeth, mouth or false teeth?	Very often ☐1	Fairly often ☐2	Occasionally ☐3	Hardly ever ☐4	Never ☐5
J3. … have you had **painful aching** in your mouth?	Very often ☐1	Fairly often ☐2	Occasionally ☐3	Hardly ever ☐4	Never ☐5
J4. … have you found it **uncomfortable to eat any foods** because of problems with your teeth, mouth or false teeth?	Very often ☐1	Fairly often ☐2	Occasionally ☐3	Hardly ever ☐4	Never ☐5
J5. … have you been **self-conscious** because of problems with your teeth, mouth or false teeth?	Very often ☐1	Fairly often ☐2	Occasionally ☐3	Hardly ever ☐4	Never ☐5
J6. … have you **felt tense** because of problems with your teeth, mouth or false teeth?	Very often ☐1	Fairly often ☐2	Occasionally ☐3	Hardly ever ☐4	Never ☐5
J7. … has your **diet been unsatisfactory** because of problems with your teeth, mouth or false teeth?	Very often ☐1	Fairly often ☐2	Occasionally ☐3	Hardly ever ☐4	Never ☐5
J8. … have you had to **interrupt meals** because of problems with your teeth, mouth or false teeth?	Very often ☐1	Fairly often ☐2	Occasionally ☐3	Hardly ever ☐4	Never ☐5

G9. When you receive oral sex, how often is a condom or dental dam used? ('Dental dam' refers to a thin square piece of latex used for protection during oral-vaginal or oral-anal sex)	Never ☐1	Seldom ☐2	Occasionally ☐3	Frequently ☐4	Very frequently ☐5	Always ☐6

G10. Have you ever had sexual intercourse with another person? ('Sexual intercourse' refers to vaginal intercourse and anal intercourse only. 'Sexual intercourse' does not refer to oral sex)	No (go to G13) ☐1	Yes (go to next question) ☐2
G11.a How old were you when you first had sexual intercourse?	<16yrs (go to G12) ☐1	=/ >16yrs (go to G11b) ☐2
G11.b How old? (if =/ > 16yrs)	☐☐ Years	

G12. Altogether, in your life so far, how many people have you had sexual intercourse with?	None ☐1	1 ☐2	2 to 3 ☐3	4 to 7 ☐4	8 to 15 ☐5	16 to 28 ☐6	29 or more ☐7

G13. In your lifetime, who have you had sexual contact with?	Men only ☐1	Mostly men, sometimes women ☐2	Equally men and women ☐3	Women only ☐4	Mostly women, sometimes men ☐5

G14. How would you describe your current relationship status?	Currently in stable, long-term relationship ☐1	Currently in short-term relationships ☐2	Currently single ☐3

H. SELF-RATED HEALTH

H1. Would you rate your general health as:	Excellent ☐1	Very good ☐2	Good ☐3	Fair ☐4	Poor ☐5
H2. Would you rate your oral health as:	Excellent ☐1	Very good ☐2	Good ☐3	Fair ☐4	Poor ☐5

I. DENTAL BEHAVIOURS

I1. When did you last see a dentist:	Less than one year ago ☐1	More than one year ago ☐2
I2. What is your usual reason for seeing a dentist:	Problem ☐1	Check-up ☐2

I3. During the last year, have you not gone to the dentist because of cost:	Yes ☐1		No ☐2		
I4. How hard would it be for you to pay a $100 dental bill:	Not hard at all ☐1	Not very hard ☐2	A little bit hard ☐1	Very hard ☐2	Could not pay ☐2

J. THE QUESTIONS BELOW ASK ABOUT TROUBLES THAT PEOPLE MAY HAVE IN DAILY LIFE BECAUSE OF DENTAL PROBLEMS.

How often during the last year….	**Please tick ONE box that best describes your experience**				
J1. … have you had trouble **pronouncing (or saying)** any **words** because of problems with your teeth, mouth or false teeth?	Very often ☐1	Fairly often ☐2	Occasionally ☐3	Hardly ever ☐4	Never ☐5
J2. … have you felt that your **sense of taste** has worsened because of problems with your teeth, mouth or false teeth?	Very often ☐1	Fairly often ☐2	Occasionally ☐3	Hardly ever ☐4	Never ☐5
J3. … have you had **painful aching** in your mouth?	Very often ☐1	Fairly often ☐2	Occasionally ☐3	Hardly ever ☐4	Never ☐5
J4. … have you found it **uncomfortable to eat any foods** because of problems with your teeth, mouth or false teeth?	Very often ☐1	Fairly often ☐2	Occasionally ☐3	Hardly ever ☐4	Never ☐5
J5. … have you been **self-conscious** because of problems with your teeth, mouth or false teeth?	Very often ☐1	Fairly often ☐2	Occasionally ☐3	Hardly ever ☐4	Never ☐5
J6. … have you **felt tense** because of problems with your teeth, mouth or false teeth?	Very often ☐1	Fairly often ☐2	Occasionally ☐3	Hardly ever ☐4	Never ☐5
J7. … has your **diet been unsatisfactory** because of problems with your teeth, mouth or false teeth?	Very often ☐1	Fairly often ☐2	Occasionally ☐3	Hardly ever ☐4	Never ☐5
J8. … have you had to **interrupt meals** because of problems with your teeth, mouth or false teeth?	Very often ☐1	Fairly often ☐2	Occasionally ☐3	Hardly ever ☐4	Never ☐5

M. THIS SECTION ASKS ABOUT YOUR CULTURAL IDENTIFY AND EXPERIENCES OF RACISM OR DISCRIMINATION.

M1. Do you know a lot about your Aboriginal/Torres Strait Islander culture?	Lots ☐1	Fair bit ☐2	Little bit ☐3	Not much ☐4
M2. Do you identify with a tribal group, a language group or clan?	Yes (Specify_____) ☐1		No ☐2	Don't know ☐3
M3. To you, is being Aboriginal/Torres Strait Islander…	The most important thing (central to who you are) ☐1	Important, but not the only thing ☐2	Something you don't know enough about and want to know more about ☐3	Something you don't think about ☐4
M4. Do you feel like you know a lot about white fella ways?	Lots ☐1	Fair bit ☐2	Little bit ☐3	Not much ☐4
M5. Do you have a strong family who help each other?	Always ☐1	Most times ☐2	Sometimes ☐3	Not really ☐4

N. IN THE LAST 12 MONTHS, HAVE YOU EVER FELT THAT YOU HAVE BEEN TREATED UNFAIRLY IN ANY OF THE FOLLOWING WAYS BECAUSE OF YOUR IDENTITY AS AN ABORIGINAL/TORRES STRAIT ISLANDER PERSON.

	Strongly Disagree →				Strongly Agree
N.1 Applying for work or when at work.	☐1	☐2	☐3	☐4	☐5
N.2 At home, by neighbours, or at somebody else's house.	☐1	☐2	☐3	☐4	☐5
N.3 At school, university, training course, or other educational setting.	☐1	☐2	☐3	☐4	☐5
N.4 While doing any sporting, recreational or leisure activities.	☐1	☐2	☐3	☐4	☐5
N.5 By the police, security people, lawyers or in a court of law.	☐1	☐2	☐3	☐4	☐5
N.6 By doctors, dentists, nurses or other staff at hospitals, dental clinics or doctor surgeries.	☐1	☐2	☐3	☐4	☐5
N.7 By staff of government agencies.	☐1	☐2	☐3	☐4	☐5
N.8 When seeking any other services.	☐1	☐2	☐3	☐4	☐5
N.9 By members of the general public.	☐1	☐2	☐3	☐4	☐5
N.10 Any other situation. (*please specify*) _____	☐1	☐2	☐3	☐4	☐5

O. PAIN. THIS SECTION ASKS ABOUT YOUR EXPERIENCES OF PAIN BOTH NOW AND IN THE COURSE OF YOUR LIFE.

O1. Do you now have significant pain that has lasted 6 months or more? ***If NO, skip to O2***	Yes ☐1	No ☐2
O1a. How severe would you rate that pain, on a scale from 0-100, with 0 being "no pain" and 100 being "the maximum pain possible"?	Write the number in this box	
O1b. How long has this pain lasted?	Write the number in this box	
O1c. How many days a week do you experience this pain?	Write the number in this box	
O1d. What is the source of this pain?	Write the answer in this box	

O2. Do you have any other significant pain now that has lasted 6 months or more? ***If NO, skip to O3***	Yes ☐1	No ☐2

O2a. How severe would you rate that pain, on a scale from 0-100 with 0 being "no pain" and 100 being "the maximum pain possible"?		Write the number in this box
O2b. How long has this pain lasted?		Write the number in this box
O2c How many days a week do you experience this pain?		Write the number in this box
O2d. What is the source of this pain?		Write the answer in this box

O3. Do you now have significant pain that has lasted less than 6 months? ***If NO, skip to O4***	Yes ☐1	No ☐2
O3a. How severe would you rate that pain, on a scale from 0-100 with 0 being "no pain" and 100 being "the maximum pain possible"?		Write the number in this box
O3b. How long has this pain lasted?		Write the number in this box
O3c. How many days a week do you experience this pain?		Write the number in this box
O3d. what is the source of this pain?		Write the answer in this box

O4. Besides any pain just discussed, have you ever had significant pain? ***If NO, skip to section P***	Yes ☐1	No ☐2
O4a. How severe would you rate that pain, on a scale from 0-100 with 0 being "no pain" and 100 being "the maximum pain possible"?		Write the number in this box
O4b. How long has this pain lasted?		Write the number in this box
O4c. How many days a week do you experience this pain?		Write the number in this box
O4d. What is the source of this pain?		Write the answer in this box

P. FEAR OF PAIN: THIS SECTION HAS QUESTIONS ASKING ABOUT ANY FEAR OF PAIN THAT YOU MIGHT EXPERIENCE. THE ITEMS LISTED BELOW DESCRIBE PAINFUL EXPERIENCES. PLEASE LOOK AT EACH ITEM AND THINK ABOUT HOW FEARFUL YOU ARE OF EXPERIENCING THE PAIN ASSOCIATED WITH EACH ITEM. IF YOU HAVE NEVER EXPERIENCED THE PAIN OF A PARTICULAR ITEM, PLEASE ANSWER ON THE BASIS OF HOW FEARFUL YOU EXPECT YOU WOULD BE IF YOU HAD SUCH AN EXPERIENCE. CIRCLE ONE NUMBER FOR EACH ITEM BELOW TO RATE YOUR FEAR OF PAIN IN RELATION TO EACH EVENT.

I FEAR THE PAIN associated with:

P1. Breaking your arm	Not at all ☐1	A little ☐2	A fair amount ☐3	Very much ☐4	Extreme ☐5
P2. Having a foot doctor remove a wart from your foot with a sharp instrument.	Not at all ☐1	A little ☐2	A fair amount ☐3	Very much ☐4	Extreme ☐5
P3. Getting a paper-cut on your finger.	Not at all ☐1	A little ☐2	A fair amount ☐3	Very much ☐4	Extreme ☐5
P4. Receiving an injection in your mouth.	Not at all ☐1	A little ☐2	A fair amount ☐3	Very much ☐4	Extreme ☐5
P5. Getting strong soap in both your eyes while bathing and showering.	Not at all ☐1	A little ☐2	A fair amount ☐3	Very much ☐4	Extreme ☐5
P6. Having someone slam a heavy car door on your hand.	Not at all ☐1	A little ☐2	A fair amount ☐3	Very much ☐4	Extreme ☐5
P7. Gulping a hot drink before it has cooled.	Not at all ☐1	A little ☐2	A fair amount ☐3	Very much ☐4	Extreme ☐5
P8. Receiving an injection in your hip/buttocks.	Not at all ☐1	A little ☐2	A fair amount ☐3	Very much ☐4	Extreme ☐5
P9. Falling down a flight of concrete stairs.	Not at all ☐1	A little ☐2	A fair amount ☐3	Very much ☐4	Extreme ☐5

13.2 Appendix B: 12-month Follow-up Questionnaire

AUSTRALIAN RESEARCH CENTRE FOR POPULATION ORAL HEALTH
ADELAIDE DENTAL SCHOOL

HPV and OROPHARYNGEAL CANCER (THROAT CANCER) STUDY

12 month follow-up – Male & Female

1. Participant ID Number_____
2. Interviewer name_____
3. Date of interview (dd/mm/yy)_ _____
4. Date of birth (dd/mm/yy)_____
5. Sex: Male/Female/Other _____

Please answer ALL of the sections in the survey, even if they do not seem to be directly relevant to *you*. Everything you tell us will be treated in strict confidence but you are free to leave any specific questions that you do not wish to answer.

If you are not sure of the correct answer, please give us your best estimate. We are asking many different people the same sets of questions and we are very interested in the different types of responses.

A. PLEASE LOOK AT THESE STATEMENTS AND SAY WHETHER YOU THINK EACH ONE IS TRUE OR FALSE			
A1. HPV is very rare	True ☐1	False ☐2	Don't know ☐3
A2. HPV always has visible signs or symptoms	True ☐1	False ☐2	Don't know ☐3
A3. HPV can be passed on by genital skin-to-skin contact	True ☐1	False ☐2	Don't know ☐3
A4. There are many types of HPV	True ☐1	False ☐2	Don't know ☐3
A5. HPV can be passed on during sexual intercourse	True ☐1	False ☐2	Don't know ☐3
A6. Men cannot get HPV	True ☐1	False ☐2	Don't know ☐3
A7. HPV usually doesn't need any treatment	True ☐1	False ☐2	Don't know ☐3
A8. Most sexually active people will get HPV at some point in their lives	True ☐1	False ☐2	Don't know ☐3
A9. A person could have HPV for many years without knowing it	True ☐1	False ☐2	Don't know ☐3
A10. HPV can cause cancer in men	True ☐1	False ☐2	Don't know ☐3

B. WE ARE INTERESTED IN UNDERSTANDING HOW YOU ARE FEELING IN TERMS OF YOUR WELL BEING SO THE FOLLOWING SECTION INCLUDES QUESTIONS ABOUT YOUR MENTAL HEALTH AND ANY ANXIETY OR DISTRESS YOU MAY BE EXPERIENCING.

B1. I feel calm	Not at all ☐1	Somewhat ☐2	Moderately ☐3	Very much so ☐4
B2. I feel tense	Not at all ☐1	Somewhat ☐2	Moderately ☐3	Very much so ☐4
B3. I feel upset	Not at all ☐1	Somewhat ☐2	Moderately ☐3	Very much so ☐4
B4. I feel relaxed	Not at all ☐1	Somewhat ☐2	Moderately ☐3	Very much so ☐4
B5. I feel content	Not at all ☐1	Somewhat ☐2	Moderately ☐3	Very much so ☐4
B6. I feel worried	Not at all ☐1	Somewhat ☐2	Moderately ☐3	Very much so ☐4

Have you recently.....	**Please tick ONE box that best describes your experience**			
B7. Been able to concentrate on what you are doing?	Better than usual ☐1	Same as usual ☐2	Less than usual ☐3	Much less than usual ☐4
B8. Lost much sleep over worry?	Not at all ☐1	No more than usual ☐2	Rather more than usual ☐3	Much more than usual ☐4
B9. Felt that you are playing a useful part in things?	More so than usual ☐1	Same as usual ☐2	Less useful than usual ☐3	Much less useful ☐4
B10. Felt capable of making decisions about things?	More so than usual ☐1	Same as usual ☐2	Less than usual ☐3	Much less than capable ☐4
B11. Felt constantly under strain?	Not at all ☐1	No more than usual ☐2	Rather more than usual ☐3	Much more than usual ☐4
B12. Felt you couldn't overcome your difficulties?	Not at all ☐1	No more than usual ☐2	Rather more than usual ☐3	Much less than usual ☐4
B13. Been able to face up to your problems?	More so than usual ☐1	Same as usual ☐2	Less able than usual ☐3	Much less than usual ☐4
B14. Been feeling unhappy and depressed?	Not at all ☐1	No more than usual ☐2	Rather more than usual ☐3	Much more than usual ☐4
B15. Been losing confidence in myself?	Not at all ☐1	No more than usual ☐2	Rather more than usual ☐3	Much more than usual ☐4
B16. Been thinking of myself as a worthless person?	Not at all ☐1	No more than usual ☐2	Rather more than usual ☐3	Much more than usual ☐4
B17. Been feeling reasonably happy, all things considered?	More so than usual ☐1	About the same as usual ☐2	Less than usual ☐3	Much less than usual ☐4

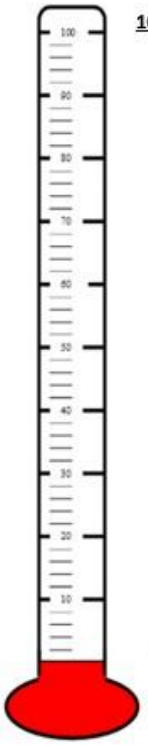
C. THIS SECTION ASKS ABOUT YOUR GENERAL QUALITY OF LIFE. WHICH OF THE FOLLOWING STATEMENTS BEST DESCRIBES YOUR HEALTH TODAY:

Under each heading, please tick ONE box that describes your health TODAY

C1. Mobility	I have no problems in walking about ☐1	I have slight problems in walking about ☐2	I have moderate problems in walking about ☐3	I have severe problems in walking about ☐4	I am unable to walk about ☐5

C2. Self-care	I have no problems washing or dressing myself ☐1	I have slight problems washing or dressing myself ☐2	I have moderate problems washing or dressing myself ☐3	I have severe problems washing or dressing myself ☐4	I am unable to wash or dress myself ☐5
C3. Usual activities (for example – work, study, housework, family or leisure activities)	I have no problems doing my usual activities ☐1	I have slight problems doing my usual activities ☐2	I have moderate problems doing my usual activities ☐3	I have severe problems doing my usual activities ☐4	I am unable to do my usual activities ☐5
C4. Pain/Discomfort	I have no pain or discomfort ☐1	I have slight pain or discomfort ☐2	I have moderate pain or discomfort ☐3	I have severe pain or discomfort ☐4	I have extreme pain or discomfort ☐5
C5. Anxiety/Depression	I am not anxious or depressed ☐1	I am slightly anxious or depressed ☐2	I am moderately anxious or depressed ☐3	I am severely anxious or depressed ☐4	I am extremely anxious or depressed ☐5

The health thermometer



100 = best health

0 = worst health

C6. **Health thermometer**

We would like to know how good or bad your health is **TODAY.**

This scale is numbered from 0 to 100.

100 means the best health you can imagine.

0 means the worst health you can imagine.

How would you rate your health today?

Please write the number you marked on the scale in the box below.

C7. Before today, had you ever heard of HPV (human papillomavirus)?	Yes ☐1	No ☐2	Not sure ☐3			
C8. Do you think your knowledge about HPV is:	Never heard of HPV ☐1	Very poor ☐2	Poor ☐3	Fair ☐4	Good ☐5	Very good ☐6
C9. Do you have any unanswered questions about HPV?	Yes ☐1 Please state: _____ _____ _____	No ☐2				

D. THIS SECTION ASKS QUESTIONS ABOUT YOUR CERVICAL SCREENING TESTS/ PAP SMEAR RESULTS

(FEMALE'S ONLY)

D1. Compared with other women the same age as you, do you think your chances of developing cervical cancer in the next ten years are...	Much below average ☐1	A little below average ☐2	Average for women my age ☐3	A little above average ☐4	Much above average ☐5	Prefer not to answer ☐6

E. THESE QUESTIONS ARE ABOUT THE HPV VACCINATION: *BOTH BOYS AND GIRLS CAN RECEIVE THE HPV VACCINE*

E1. Which of the following statements best describes whether you have had the HPV vaccine (also called the human papillomavirus vaccine, cervical cancer vaccine, Gardasil or Cervarix vaccine)?

Please select only ONE option

Yes, I had 1 dose of the HPV vaccine ☐1	Yes, I had 2 doses of the HPV vaccine ☐2	Yes, I had 3 doses of the HPV vaccine ☐3	Yes I have but I am not sure how many doses I received ☐4	No, I was offered the HPV vaccine, but I did not have it ☐5 *(Go to F1)*	No, I have never been offered the HPV vaccine ☐6 *(Go to F1)*	I don't know ☐7 *(Go to F1)*
Any comments?						

E2. Where did you receive your HPV vaccine (also called the human papillomavirus vaccine, cervical cancer vaccine, Gardasil or Cervarix vaccine)?

Please select only ONE option for each dose

1st dose

School ☐1	General practitioner/practice nurse ☐2	Family Planning Clinic ☐3	Specialist doctor ☐4	Can't remember ☐5	Other: ☐6 Please specify: _____

2nd dose					
School ☐1	General practitioner/practice nurse ☐2	Family Planning Clinic ☐3	Specialist doctor ☐4	Can't remember ☐5	Other: ☐6 Please specify: _____
3rd dose					
School ☐1	General practitioner/practice nurse ☐2	Family Planning Clinic ☐3	Specialist doctor ☐4	Can't remember ☐5	Other: ☐6 Please specify: _____

E3. Which years were you vaccinated with the HPV vaccine (also called human papillomavirus vaccine, cervical cancer vaccine, Gardasil or Cervarix vaccine)? (e.g. 2002)

The HPV vaccine first became available free for girls in year 7 in Australia from 2007 and this is ongoing. It was also available free of charge to women aged up to 26 years from 2007 until the end of 2009. The vaccine was available for boys from 2013.

1st dose							Can't remember ☐1
2nd dose							Can't remember ☐1
3rd dose							Can't remember ☐1

F. CERVICAL SCREENING AND FAMILY HISTORY *(FEMALES ONLY)*

F1. How old were you when you had your first pap test?	☐ Years	Can't remember ☐1

G. HEALTH AND LIFESTYLE

G1. Have you ever been a regular smoker?	Yes ☐1	No ☐2 *(Go to G7)*
*If you **currently** smoke cigarettes please answer Q G2–Q G3*		
G2. How old were you when you started smoking regularly?	☐ Years	Can't remember ☐1
G3. On a usual day how many cigarettes do you smoke?	☐ Write the number in this box	
*If you are a **former** smoker please answer Q G4 –Q G6*		
G4. How long ago did you stop smoking cigarettes?	☐ Years ☐ Months	
G5. For how long had you smoked cigarettes?	☐ Years ☐ Months	
G6. On a usual day, how many cigarettes did you smoke?	☐ Write the number in this box	

G7. About how many hours **per week** are you exposed to someone else's tobacco smoke?	At home ☐ Hours	In other places (e.g. going out, in cars, at work) ☐ Hours

G8. In the **last 7 days** how many **times** have you done the following activities?	
Walking continuously, for at least 10 minutes	☐ **times in the last week**
Vigorous physical activity *(that made you breathe harder of puff and pant, like jogging, cycling etc. but **not** household chores or gardening)*	☐ **times in the last week**
Moderate physical activity *(gentle swimming, social tennis, vigorous gardening or work around the house, yoga etc.)*	☐ **times in the last week**

G9. If you add up all the time you spent doing each activity **last week**, how much **time (total hours/minutes)** did you spend **altogether** doing each type of activity?	
Walking continuously, for at least 10 minutes	**Hours : minutes** ☐
Vigorous physical activity *(that made you breathe harder of puff and pant, like jogging, cycling etc. but **not** household chores or gardening)*	**Hours : minutes** ☐
Moderate physical activity *(gentle swimming, social tennis, vigorous gardening or work around the house, yoga etc.)*	**Hours : minutes** ☐

G10. How often do you drink alcohol?

Every day	5–6 times per week	3–4 times per week	2 days a week	1 day a week	2–3 times a month	Once a month	On special occasions	Ex-drinker	I have never drank any alcohol
☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐8	☐9	☐10 *(Go to G15)*

G11. If you are an ex-drinker, how old were you when you stopped?	☐ years old

G12. During the last 12 months, how many alcoholic drinks did you have on a typical day when you drank alcohol?	☐ number of drinks

G13. During the last 12 months, how often did you have 4 or more drinks containing any alcohol within a 2 hour period?

I have never drank more than 4 drinks in 2 hours	1–2 days in the past year	3–11 days in the past year	1 day a month	2–3 days a month	1 days a week	2 days a week	3–4 days a week	5–6 days a week	Every day
☐1	☐2	☐3	☐4	☐5	☐6	☐7	☐8	☐9	☐10

G14. During the last 12 months, what is the largest number of alcoholic drinks you have drank within a 24-hour period?						
1–3 drinks ☐1	4–5 drinks ☐2	5–7 drinks ☐3	8–11 drinks ☐4	12–17 drinks ☐5	18–23 drinks ☐6	24+ drinks ☐7

G15. Have you ever injected any drugs not prescribed by a physician? *(e.g. ice, heroin, speed, cocaine, ecstasy, steroids or any recreational drugs)*	No ☐1	Yes ☐2
G16. Have you ever taken any drugs not prescribed by a physician? *(e.g. ice, heroin, speed, cocaine, ecstacy, steroids or any recreational drugs)*	No ☐1	Yes ☐2

G17. Since we saw you last year, have you made any changes to the following health behaviours?			
G17a. Tobacco smoking	No ☐1	Yes ☐2	If Yes, what changes? _____
G17b. Alcohol consumption	No ☐1	Yes ☐2	If Yes, what changes? _____
G17c. Non-prescription drugs Eg marijuana	No ☐1	Yes ☐2	If Yes, what changes? _____
G17d. Sexual health	No ☐1	Yes ☐2	If Yes, what changes? _____
G17e. Other	No ☐1	Yes ☐2	If Yes, what changes? _____

H. THE NEXT SECTION ASKS QUESTIONS ON IMPORTANT EVENTS THAT MIGHT HAVE OCCURRED IN YOUR LIFE THAT IMPACT YOUR HEALTH.

In the last **12 months** please tick if you or anyone else in your family has experienced any of the following:

H1.Incarceration	Yes ☐1	No ☐2	H2.Domestic violence	Yes ☐1	No ☐2
H3.Death	Yes ☐1	No ☐2	H4.Drug/alcohol abuse	Yes ☐1	No ☐2
H5.Child removal	Yes ☐1	No ☐2	H6.Racism	Yes ☐1	No ☐2
H7.Psychological Distress (depression/anxiety)	Yes ☐1	No ☐2	H8.Cultural/spiritual pain	Yes ☐1	No ☐2
H9a. Other	Yes ☐1	No ☐2	H9b.If other, please describe:		

I. THE FOLLOWING SECTION INCLUDES QUESTIONS ABOUT HOW IMPORTANT THINGS RELATING TO ABORIGINAL CULTURE ARE TO YOU.					
I1. Identifying as Aboriginal	Strongly agree ☐1	Agree ☐2	Neither agree not diasgree ☐3	Disagree ☐4	Strongly disagree ☐5
I2. Aboriginal social networks/community	Strongly agree ☐1	Agree ☐2	Neither agree not diasgree ☐3	Disagree ☐4	Strongly disagree ☐5
I3. Acknowledging historical consequence of colonisation	Strongly agree ☐1	Agree ☐2	Neither agree not diasgree ☐3	Disagree ☐4	Strongly disagree ☐5
I4. Addressing racism	Strongly agree ☐1	Agree ☐2	Neither agree not diasgree ☐3	Disagree ☐4	Strongly disagree ☐5
I5. Addressing social disadvantage (being poor)	Strongly agree ☐1	Agree ☐2	Neither agree not diasgree ☐3	Disagree ☐4	Strongly disagree ☐5
I6. Addressing psychological distress (depression/anxiety)	Strongly agree ☐1	Agree ☐2	Neither agree not diasgree ☐3	Disagree ☐4	Strongly disagree ☐5
I7. Connection to country	Strongly agree ☐1	Agree ☐2	Neither agree not diasgree ☐3	Disagree ☐4	Strongly disagree ☐5
I8. Communication between Aboriginal and non-Aboriginal people	Strongly agree ☐1	Agree ☐2	Neither agree not diasgree ☐3	Disagree ☐4	Strongly disagree ☐5
I9. Spirituality	Strongly agree ☐1	Agree ☐2	Neither agree not diasgree ☐3	Disagree ☐4	Strongly disagree ☐5
I10. Other (please state)	Strongly agree ☐1	Agree ☐2	Neither agree not diasgree ☐3	Disagree ☐4	Strongly disagree ☐5

J. THIS SECTION ASKS QUESTIONS ABOUT PAIN.		
J1. Are you currently taking any medication for pain?	Yes ☐1	No ☐2

J2. Which of the following medications are you currently taking for your pain? *Please tick all that apply*

Advil	Nurofen	Panadol	Alprazolam	Tramadol	Don't know	Other
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7

J3. How helpful have the pain medications been in relieving your pain?

The medications have helped reduce my pain a little bit	The medications have helped reduce my pain a lot	The medications have helped reduce my pain nearly to half	The medications have helped reduce my pain to just a discomfort	I feel no pain when I take the medications
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

J4. Are you experiencing any pain now?	Yes ☐ 1	No ☐ 2 *(Go to J18)*

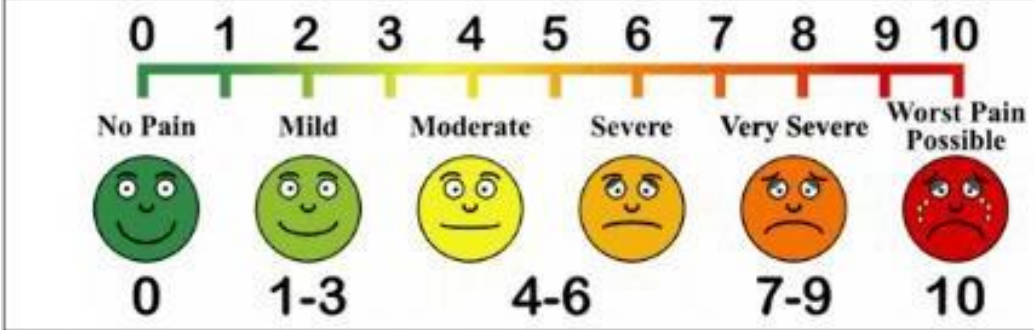
J5. If yes, how long have you experienced this pain?

Number of weeks/months/years

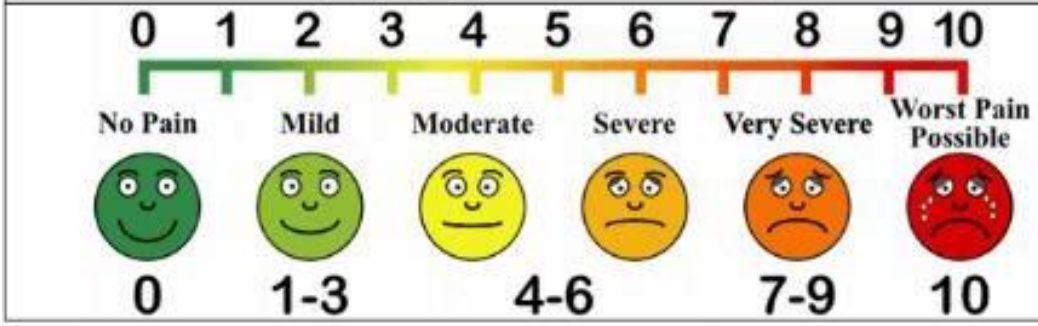
J6. Please select the location of your pain from the below options. *(select all that apply)*

Head/ Face/ Mouth/ Jaw Teeth	Neck	Chest/ Upper Back/ Lower Back	Hands/ Wrists/ Fingers	Stomach (upper/ middle/ lower)	Hips/Pelvic region	Legs/ Calves/ Shin/ Ankle joints/ Heel/ Toes	Whole body
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8

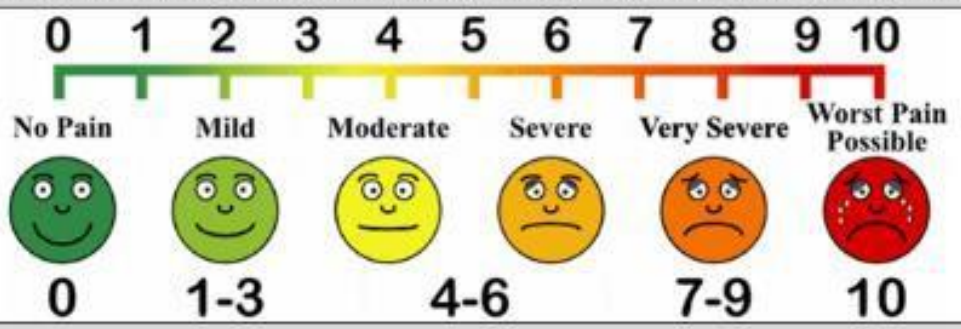
J7. Over the last **24 hours**, what has been your average pain? *Please circle a number in the picture below.*



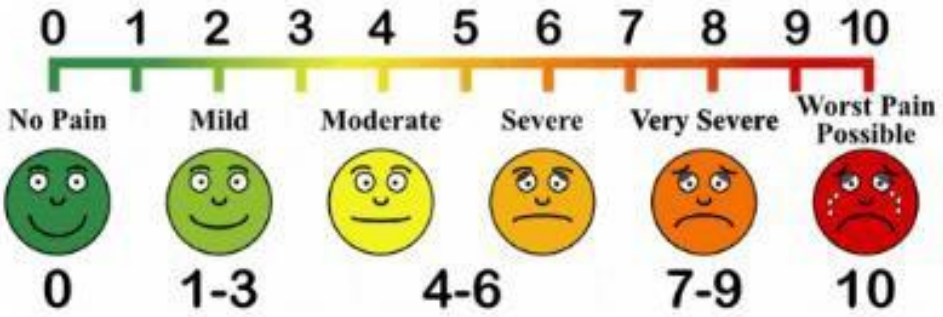
J8. What is the current level of your pain **now**? *Please circle a number in the picture below.*



J9. Over the last **24 hours**, what has been your **worst level of pain**? *Please circle a number in the picture below.*



J10. What was the **least level of pain** in the last **24 hours**? *Please circle a number in the picture below.*



J11. Please select the words below that describe your pain and its intensity: *Select as many that apply*

Throbbing	Stabbing	Aching	Burning	Pricking	Pulling	Shooting	Numbing	Other
☐	☐	☐	☐	☐	☐	☐	☐	☐

J12. Has your pain stopped you from working? *Select **ONE** option from the choices below*

My pain does not stop me from working	My pain causes little discomfort when I'm working	My pain limits my ability to work, but I still manage to work if I take breaks and help from others	My pain severely limits my ability to work and I struggle to work even with breaks and help	I am currently not working because of my pain
☐	☐	☐	☐	☐

J13. How much has your pain interfered with your appetite?

My pain does not interfere with my appetite	My pain has reduced my appetite a little	My appetite changes more frequently because of my pain	I often forget to eat because of my pain	I have no appetite because of my pain
☐	☐	☐	☐	☐

J14. How much has your pain interfered with your routine daily?

My pain does not interfere with my daily routine	I have to change my daily routine a little if I am in pain	I have to change my daily routine a lot if I am in pain	I avoid most of my daily tasks if I am in pain	I stay in bed if I am in pain
☐	☐	☐	☐	☐

J15. How much has your pain interfered with your social activites?				
My pain does not interfere with my social activites ☐1	My pain has reduced my social engagements/life a little ☐2	My pain has significantly changed my social activities ☐3	I avoid social activities because of my pain ☐4	I have no social activities because of my pain ☐5

J16. How much has your pain interfered with your outdoor or fun activities?				
My pain does not interfere with my outdoor activites ☐1	My pain has reduced my outdoor activities a little ☐2	My pain has significantly changed my outdoor activities ☐3	I avoid outdoor activities because of my pain ☐4	I have no outdoor activities because of my pain ☐5

J17. How much has your pain interfered with your sexual activities?				
My pain does not interfere with my sexual activites ☐1	My pain has reduced my sexual activities a little ☐2	My pain has significantly changed sexual activities ☐3	I avoid sexual activities because of my pain ☐4	I have no sexual activities because of my pain ☐5

J18. How much has your pain interfered with your sleep?				
My pain does not interfere with my sleep ☐1	My pain has reduced my sleep a little ☐2	My pain has significantly affected my sleeping pattern ☐3	I wake up every few hours if I am in pain ☐4	I cannot fall asleep when I am in pain ☐5

J19. How depressed and anxious have you been?				
I have not experienced anxiety/ low mood/ sadness/ stress/ depression ☐1	I have been a little anxious/ sad/ worried/ stressed/ depressed ☐2	I have been feeling worried/ sad/ anxious/ stressed/ depressed a lot ☐3	I have been feeling worried/ sad/ anxious/ stressed/ depressed all the time ☐4	I am unable to function (work, sleep, eat, enjoy life) because I feel extremely worried/ sad/ anxious/ stressed/ depressed most of the time ☐5

K. FEAR OF PAIN: THIS SECTION HAS QUESTIONS ASKING ABOUT ANY FEAR OF PAIN THAT YOU MIGHT EXPERIENCE.

The items listed below describe painful experiences. Please look at each item and think about how fearful you are of experiencing the pain associated with each item. If you have never experienced the pain of a particular item, please answer on the basis of how fearful you expect you would be if you had such an experience.

I FEAR THE PAIN ASSOCIATED WITH:

K1. Breaking your arm	Not at all ☐1	A little ☐2	A fair amount ☐3	Very much ☐4	Extremely ☐5
K2. Having a foot doctor remove a wart from your foot with a sharp instrument.	Not at all ☐1	A little ☐2	A fair amount ☐3	Very much ☐4	Extremely ☐5
K3. Getting a paper-cut on your finger.	Not at all ☐1	A little ☐2	A fair amount ☐3	Very much ☐4	Extremely ☐5

K4. Receiving an injection in your mouth.	Not at all ☐1	A little ☐2	A fair amount ☐3	Very much ☐4	Extremely ☐5
K5. Getting strong soap in both your eyes while bathing and showering.	Not at all ☐1	A little ☐2	A fair amount ☐3	Very much ☐4	Extremely ☐5
K6. Having someone slam a heavy car door on your hand.	Not at all ☐1	A little ☐2	A fair amount ☐3	Very much ☐4	Extremely ☐5
K7. Gulping a hot drink before it has cooled.	Not at all ☐1	A little ☐2	A fair amount ☐3	Very much ☐4	Extremely ☐5
K8. Receiving an injection in my hips/buttocks	Not at all ☐1	A little ☐2	A fair amount ☐3	Very much ☐4	Extremely ☐5
K9. Falling down a flight of concrete stairs	Not at all ☐1	A little ☐2	A fair amount ☐3	Very much ☐4	Extremely ☐5

THE NEXT FEW QUESTIONS ASSESS YOUR DISTRESS ABOUT PAIN

K10. Pain causes me to have strong negative feelings	Not at all ☐1	A little ☐2	A fair amount ☐3	Very much ☐4	Extremely ☐5
K11. The fact that I could feel pain in the future worries me a lot	Not at all ☐1	A little ☐2	A fair amount ☐3	Very much ☐4	Extremely ☐5
K12. I am scared of feeling pain	Not at all ☐1	A little ☐2	A fair amount ☐3	Very much ☐4	Extremely ☐5
K13. Being in pain makes me feel sad	Not at all ☐1	A little ☐2	A fair amount ☐3	Very much ☐4	Extremely ☐5

L. ORAL HEALTH. WE ARE INTERESTED IN UNDERSTANDING HOW YOU ARE FEELING ABOUT YOUR ORAL HEALTH. THE FOLLOWING SECTION INCLUDES QUESTIONS ABOUT YOUR ORAL HEALTH.

L1. Do you think you have gum disease?		Yes ☐1	No ☐2	Don't know ☐3
L2. Have you ever been told that you have lost bone around your teeth?		Yes ☐1	No ☐2	Don't know ☐3
L3. Have you ever received the following treatment: scaling and root planing?		Yes ☐1	No ☐2	Don't know ☐3
L4. Have you ever had any teeth become loose on their own, without an injury?		Yes ☐1	No ☐2	Don't know ☐3
L5. How often during the last 7 days did you use mouth wash or any dental rinse product?	1–6 times ☐1	> 7 times ☐2	Never ☐3	Don't know ☐4

L6. How often during the last 7 days did you use dental floss, tape or an interdental brush to clean between your teeth, other than just to remove food particles stuck between your teeth?	1–6 times ☐1	> 7 times ☐2	Never ☐3	Don't know ☐4
L7. During the past three months have you noticed that you have a tooth that doesn't look right?		Yes ☐1	No ☐2	Don't know ☐3

L8. How would you rate the health of your GUMS? Would you say that it is…	Excellent ☐1	Very good ☐2	Good ☐3	Fair ☐4	Poor ☐5	Don't know ☐6

THANK YOU FOR TAKING THE TIME TO ANSWER OUR QUESTIONS

PLEASE SHARE ANYTHING ELSE YOU WOULD LIKE TO TELL US IN THE SPACE BELOW.

13.3 Appendix C: Protocol for the HPV-OPC project

JMIR RESEARCH PROTOCOLS Jamieson et al

Protocol

Human Papillomavirus and Oropharyngeal Cancer Among Indigenous Australians: Protocol for a Prevalence Study of Oral-Related Human Papillomavirus and Cost-Effectiveness of Prevention

Lisa Jamieson[1], PhD; Gail Garvey[2], PhD; Joanne Hedges[1], MPH; Amanda Mitchell[3], MPH; Terry Dunbar[4], PhD; Cathy Leane[5], MPH; Isaac Hill[3], MPH; Kate Warren[6], MPH; Alex Brown[7], PhD; Xiangqun Ju[1], PhD; David Roder[8], DDSc; Richard Logan[9], PhD; Newell Johnson[10], PhD; Megan Smith[11], PhD; Annika Antonsson[12], PhD; Karen Canfell[11], PhD

[1]Australian Research Centre for Population Oral Health, Adelaide Dental School, University of Adelaide, Adelaide, Australia
[2]Menzies School of Health Research, Charles Darwin University, Darwin, Australia
[3]Aboriginal Health Council of South Australia, Adelaide, Australia
[4]Yaitya Purruna Indigenous Health Unit, University of Adelaide, Adelaide, Australia
[5]Aboriginal Health Division Women's and Children's Health Network, Adelaide, Australia
[6]Pika Wiya Health Service Inc, Port Augusta, Australia
[7]Wardliparingga Aboriginal Research Unit, South Australian Health & Medical Research Institute, Adelaide, Australia
[8]School of Health Sciences, Univesity of South Australia, Adelaide, Australia
[9]Adelaide Dental School, University of Adelaide, Adelaide, Australia
[10]Menzies Health Institute, Griffith University, Gold Coast, Australia
[11]Cancer Council of New South Wales, Sydney, Australia
[12]QIMR Berghofer Medical Research Institute, QIMR Berghofer Medical Research Institute, Brisbane, Australia

Corresponding Author:
Lisa Jamieson, PhD
Australian Research Centre for Population Oral Health
Adelaide Dental School
University of Adelaide
Adelaide Health & Medical Sciences Building
Adelaide, 5005
Australia
Phone: 61 08 8313 4611
Email: lisa.jamieson@adelaide.edu.au

Abstract

Background: Oropharyngeal cancer is an important, understudied cancer affecting Aboriginal and Torres Strait Islander Australians. The human papillomavirus (HPV) is a significant risk factor for oropharyngeal cancer. Current generation HPV vaccines are effective against the 2 most common types of high-risk HPVs in cancer (hrHPVs 16/18).

Objectives: This study aims (1) to yield population estimates of oncogenic genotypes of HPV in the mouth and oropharynx of defined Aboriginal and Torres Strait Islander populations; (2) to estimate the proportion of oropharyngeal cancer attributable to HPV among these Australian citizens; (3) to estimate the impact of HPV vaccination as currently implemented on rates of oropharyngeal cancer among Aboriginal and Torres Strait Islander Australians; and (4) taking into account impact on oropharyngeal as well as cervical cancer, to evaluate efficacy and cost-effectiveness of targeted extended HPV vaccination to older ages, among our study population.

Methods: Our study design and operation is straightforward, with minimal impost on participants. It involves testing for carriage of hrHPV in the mouth and oropharynx among 1000 Aboriginal South Australians by simple saliva collection and with follow-up at 12 and 24 months, collection of sexual history at baseline, collection of information for estimating health state (quality-of-life)

utilities at baseline, genotyping of viruses, predictive outcome and cost-effectiveness modeling, data interpretation and development of vaccination, and follow-up management strategies driven by the Aboriginal community.

Results: Participant recruitment for this study commenced in February 2018 and enrollment is ongoing. The first results are expected to be submitted for publication in 2019.

Conclusions: The project will have a number of important outcomes. Synthesis of evidence will enable generation of estimates of the burden of oropharyngeal cancer among Aboriginal and Torres Strait Islander Australians and indicate the likely effectiveness and cost-effectiveness of prevention. This will be important for health services planning, and for Aboriginal health worker and patient education. The results will also point to important areas where research efforts should be focused to improve outcomes in Aboriginal and Torres Strait Islander Australians with oropharyngeal cancer. There will be a strong focus on community engagement and accounting for the preferences of individuals and the community in control of HPV-related cancers. The project has international relevance in that it will be the first to systematically evaluate prevention of both cervical and oropharyngeal cancer in a high-risk Indigenous population taking into account all population, testing, and surveillance options.

Registered Report Identifier: RR1-10.2196/10503

(JMIR Res Protoc 2018;7(6):e10503) doi: 10.2196/10503

KEYWORDS

Papillomaviridae; oropharyngeal neoplasms; vaccination; population

Introduction

Human Papilloma Viruses

Human papillomaviruses (HPVs) are a heterogeneous group of over 100 genotypes, being circular, double-stranded DNA viruses that grow in stratified epithelia of skin and mucous membranes. There are approximately 15 HPV types that have potential to cause cancer. Before implementation of vaccination, a restricted number of these genotypes, known as high risk or oncogenic types, were the most common sexually transmitted infection in Australia, with an estimated 4 out of 5 Australians having a high-risk HPV (hrHPV) infection at some point in their lives [1]. The most common hrHPV types are HPV-16 and HPV-18. These HPVs are a precursor to a range of cancers in both females and males (particularly cervical cancer, other anogenital cancers and oropharyngeal cancer) and are usually acquired within 2-5 years of commencing sexual activity [2]. Preventing such HPV infections is a public health priority to reduce cancer and HPV-associated complications [3].

The rate of carriage of hrHPV at a population level at sites relevant to cancer (anogenital and oropharyngeal) in Australia is difficult to characterize; most surveys have not been national or representative, and almost all have focused on females only. Although there are some general population oral HPV DNA prevalence data [4], the big gap in the knowledge base is the oral and oropharyngeal HPV prevalence in a high-risk group for oropharyngeal cancers, Aboriginal and Torres Strait Islander Australians [5].

Human Papillomavirus and Cervical Cancers

Cervical cancer is the fourth most common cancer of women internationally [6]. Virtually, all cervical cancers are attributable to infection with oncogenic genotypes of HPV [7]. In an international study, incidence of cervical cancer was found to be higher among Indigenous women than among non-Indigenous women in most countries (Australia, New Zealand, Canada, and the United States) [8]. In Australia, there are undisputedly higher rates of cervical cancer and mortality among Indigenous compared with non-Indigenous women [9].

Human Papillomavirus and Oropharyngeal Cancers

Oropharyngeal cancers include cancer of the middle part of the throat: the tonsils, posterior one-third of the tongue, and lateral and posterior walls of the oropharynx [10]. Approximately 90% of oropharyngeal cancers are squamous cell carcinomas [11]. Tobacco and heavy alcohol use, often in a background of diets poor in essential antioxidant vitamins and minerals, are major risk factors [12]. The impact of tobacco and alcohol is synergistic, ie, a person exposed to both has multiplicative, not just additive, risk [13]. Additional risk indicators include being male, older age, having infection with *Candida* or a pro-inflammatory bacteriale, or a compromised immune system [14,15]. Survival from oropharyngeal cancers is comparatively low. This is because they are frequently asymptomatic and diagnosed at a late stage. In general, more than half of all persons with oropharyngeal cancer have regional or distant metastases at diagnosis [16]. Once the cancer has metastasized, prognosis is worse than when localized. Relative 5-year survival in the United States is 82% for localized disease, 56% for regional lymph node spread, and 33% for distant metastases [17].

In addition to tobacco and alcohol, HPV has been increasingly identified as a significant risk factor for oropharyngeal cancer [18]. Both oral HPV prevalence and HPV-positive oropharyngeal cancers are associated with younger age (compared with tobacco and alcohol-related oropharyngeal cancer), sex (higher incidence in males), sexual behaviors (higher among those who have ever had oral sex), and number of sexual partners (applies particularly to men, but works both ways) [19]. These factors increase the risk of cancer development 3-to 5-fold [20]. The proportion of oropharyngeal cancers that are HPV-positive has increased over the last decade in Europe and North America to an estimated 70% [21]. Indicative data from Australia suggest a similar increase in the fraction of oropharyngeal cancers that might be attributable to HPV [22].

Burden of Oropharyngeal Cancer in Australia

Head and neck cancers (of which oropharyngeal cancer is one) have been described as being more emotionally traumatic than any other form of cancer [23,24]. Treatments can be debilitating and disfiguring, with patients frequently going on to live with chronic functional impairment in a range of areas including speech and swallowing [25]. There are substantial effects on oral health and nutrition [26], on social functioning, and on mood, with an often immediate decrease in health-related quality of life which persists long term [24]. Ariyawardana and Johnson reported that, although rates of overall lip, oral cavity, and oropharyngeal cancer declined between 1982 and 2008, presumably due to decreased alcohol and tobacco use, and potentially improved sun protection for lip cancer, they were still high [11]. When considered in isolation, rates of oropharyngeal cancer increased during this time (1.2% per annum for men, 0.8% per annum for females), possibly due to an increased incidence of HPV-related oropharyngeal cancer [11]. Hong reported that the proportion of oropharyngeal cancers which were positive for HPV DNA and p16 increased from 20.2% in 1987-1995 to 63.5% in 2006-2010 [27].

Oropharyngeal Cancer in Aboriginal and Torres Strait Islander Australians

There is little documented evidence on the incidence of oropharyngeal cancer among Aboriginal and Torres Strait Islander Australians at a national level. Johnson and colleagues reported that Indigenous persons living in Queensland (who comprise 4% of the Queensland population) were more likely than the total Queensland population to be diagnosed with certain head and neck cancers between 1997 and 2012, specifically base of tongue or tonsil or oropharynx (standardized incidence ratio=2.16; n=81) [5]. Five-year cause-specific survival estimates, adjusted for age and sex, were 75% (95% CI 74-76%) for non-Indigenous persons and 43% (95% CI 38-49%) for Indigenous persons. Similar differentials in survival were observed for cancers of the base of tongue/tonsil/oropharynx (64% vs 27%) and mouth/oral cavity (66% vs 42%) [28]. In 2003, the rate ratio of disability-adjusted life years due to oral cavity and oropharyngeal cancer among Aboriginal and Torres Strait Islander Australians was 3.8 times that reported for the total Australian population [29].

Oropharyngeal Cancer Risk Factors Among Indigenous Australians

As with the general population, alcohol and tobacco use are often cited to be significant risk factors for oropharyngeal cancer among Aboriginal and Torres Strait Islander Australians, although the population attributable fraction for HPV-related oropharyngeal cancers in this group is unknown [9]. Aboriginal and Torres Strait Islander Australians generally commence tobacco smoking at an earlier age, continue to smoke for longer, and make fewer quitting attempts than non-Indigenous Australians [30]. In 2012-2013, Aboriginal and Torres Strait Islander Australians were 2.6 times more likely than non-Indigenous Australians to be current daily smokers (40% compared with 15% after age standardization) [31].

High-Risk Human Papillomavirus Among Aboriginal and Torres Strait Islander Australians

There are currently no population estimates of carriage of hrHPV in the upper aero-digestive tract among Aboriginal and Torres Strait Islander Australians. This is a substantial deficit in the contemporary knowledge base, particularly given the higher risk for oropharyngeal cancer among this population. To determine prevalence of hrHPV, and risk factors associated with the infection among this population, data on prevalence using sensitive HPV detection methods are necessary.

Efficacy of Human Papillomavirus Vaccination

Prevention of acquiring a persistent infection with a hrHPV through vaccination is a cost-effective and life-saving intervention to decrease the burden of HPV-related cancers in Australia. Current bi- or trivalent vaccines are effective against the 2 genotypes most strongly associated with cancer (types 16 and 18), which are detected in approximately 95% of HPV-positive oropharyngeal tumors in the United States [32,33], 94% of HPV-positive oropharyngeal tumors in males in Australia [27], and approximately 70% of cervical cancer worldwide. HPV vaccination in Australia is currently provided free of charge to adolescents aged 12-13 years through a school-based program. The goal of early vaccination is to immunize before first exposure to hrHPV [34]. The efficacy and immunogenicity of hrHPV vaccines have proven excellent in several phase 2 and 3 trials involving tens of thousands of women [35]. Few subjects lost their antibodies during the 5-6 years after vaccination, with no breakthrough disease occurring among these individuals. There has been a move to a 2-dose vaccination, which means the effective vaccine coverage in the National HPV Vaccination Program Register in Australia is likely to go up (easier to deliver in 2 rather than 3 doses), although dose spacing is very important. The next generation of nonavalent vaccines [36] has also been approved and is currently under review. Importantly, there is now a growing body of evidence that current vaccines prevent HPV infection at noncervical sites, including the mouth and oropharynx [37,38].

Human Papillomavirus Vaccination Uptake in Indigenous Populations

There are no national-level data available for the uptake of HPV vaccination among Aboriginal and Torres Strait Islander Australians. Data from the first stage of the National HPV Vaccination Program (NHVP) suggest that, in Queensland, coverage among Indigenous girls aged 12-17 years compared with all girls aged 12-17 years was lower with each dose (lower by 4% for dose 1, 10% percent for dose 2, and 15% for dose 3). This pattern was not seen in the Northern Territory, where initial coverage was 17% lower among Indigenous girls, but the course completion rate among those who started vaccination was identical (84%) [39]. Both used data on genital warts, and both reported that the impact of HPV vaccination appeared to be at least as strong in young Indigenous Australians as in non-Indigenous Australians [40,41]. Although there were initially catch-up phases of the NHVP that offered publicly funded vaccination to females aged up to age 26 years and boys aged up to 15 years, these ceased in 2009 and 2014, respectively.

There is now a relatively narrow window in early adolescence when individuals can receive free vaccination; otherwise, the remainder or full vaccine course incurs an additional cost (approximately Aus $150 per dose). This is likely to be a substantial barrier to uptake among Aboriginal and Torres Strait Islander Australians, as is the possibility of culturally inappropriate, insensitive, alienating, or intimidating aspects of provision in broader health care services [42]. It is worth highlighting, however, that school-based vaccinations reduce disparities, with school retention rates among Indigenous preadolescents being reasonably high at age 12 to 13 years [43].

Efficacy of Human Papillomavirus Vaccination in Older Populations

Wheeler and colleagues [44] conducted a phase 3, double-blind, randomized controlled trial among healthy women older than 25 years to test the hypothesis that the HPV 16/18 vaccine would be efficacious in protecting against infections, cytological abnormalities, and lesions associated with HPV 16/18 and cervical intraepithelial neoplasia level 1+, irrespective of HPV type, and infection with nonvaccine types HPV 31 and HPV 45. After 7 years of follow-up, their hypothesis was proved correct. HPV vaccination is available to females aged up to 45 years and males aged up to 26 years in Australia, at a cost. The level of elective uptake in females who were not eligible to receive vaccination through the publicly funded program is low (11%) [45].

Cost-Effectiveness of Human Papillomavirus Vaccination

Although population-level impact and herd effects following HPV vaccination have been widely documented, cost-effectiveness evaluations in Australia are scarce. Kulasingam et al reported on the cost-effectiveness for females, which supported the original Commonwealth Serum Laboratories application for the vaccine to be included on the National Immunization Program [46]. The cost-effectiveness evaluations that supported HPV vaccination for boys have never been published, although Smith and colleagues [47] evaluated the herd immunity benefits and incremental impact of male vaccinations on cancer, whereas Simms et al [48] evaluated whether cervical screening would remain cost-effective in women offered the next generation nonavalent HPV vaccine in 4 developed countries. To the best of our knowledge, there have been no specific cost-effectiveness evaluations of the optimal strategies for HPV vaccination in Indigenous populations (including the potential for extending vaccination to older ages)—a critical gap in the knowledge base given the higher burden of oropharyngeal and cervical cancer risk among this group.

What Are Utilities and Why Are They Important?

Utilities are fundamental values that represent the strength of an individual's preferences for specific health-related outcomes. Measuring health utilities involves 2 main steps: defining a set of health states of interest and valuing those health states. It is important to estimate utilities in relation to HPV, cervical cancer, and oropharyngeal cancer among Aboriginal and Torres Strait Islander Australians because the frame of reference regarding prevention, screening, and burden of cancer treatment is likely to differ in meaningful ways compared with the non-Indigenous population. Differences may be because of the substantial travel required for many Indigenous Australians and because of time away from family and country. There may be inherent distrust and fear of hospital systems not apparent in non-Indigenous populations, and the specific treatment-associated morbidity may be valued differently. It is important to capture this information that can be used to directly calculate quality-adjusted life years and to, in turn, be translated into health policy regarding Aboriginal patient journeys with primary and secondary prevention for cervical, other genital, and oropharyngeal cancer. Although health state valuations appropriate for modeled economic evaluations have been undertaken for cervical HPV disease including cancer and precancerous lesions [49,50] and for genital warts [51], there is a paucity of information on health state valuations for other HPV cancer states including oropharyngeal cancer. There is a particular dearth of information on HPV-related health state valuations for Aboriginal and Torres Strait Islander Australians.

Study Aims

The aims of this study were as follows:

1. To yield population estimates of the age-specific prevalence of oncogenic genotypes of HPV in the mouth and oropharynx of defined Aboriginal and Torres Strait Islander populations (male and female). *Hypothesis: The prevalence of oral HPV among Aboriginal and Torres Strait Islander Australians will be high compared with national-level estimates.*
2. Using preliminary data from Aim 1, and information on the prevalence of other risk factors for oropharyngeal cancer in the Aboriginal and Torres Strait Islander population, to estimate burden of HPV-related oropharyngeal cancer among Aboriginal and Torres Strait Islander men and women. *Hypothesis: The burden among Aboriginal and Torres Strait Islanders of HPV and related oropharyngeal cancer will be high.*
3. To estimate the impact of HPV vaccination as currently implemented on rates of cervical and oropharyngeal cancer among Aboriginal and Torres Strait Islander Australians. *Hypothesis: HPV vaccination will, over time, reduce the burden of cervical and oropharyngealcancer among Aboriginals and Torres Strait Islanders.*
4. To evaluate efficacy and cost-effectiveness of targeted extended HPV vaccination among Aboriginal and Torres Strait Islander Australians, incorporating the effectiveness against both cervical cancer (in females) and oropharyngeal cancer. Different upper age thresholds for targeted extension will be considered. *Hypothesis: Age-extended HPV vaccination for Aboriginal and Torres Strait Islander Australians will be efficacious; we will estimate an upper age limit at which it would be cost-effective.*

Methods

Study Design

Our overall study design will impose minimal impost on Aboriginal and Torres Strait Islander participants. It involves

testing for carriage of hrHPV in the mouth and oropharynx among 1000 Aboriginal South Australians by simple saliva collection, with follow-up at 12 and 24 months, collection of sexual history at baseline, collection of information for estimating utilities at baseline, genotyping the viruses, statistical analysis (including cost-effectiveness modeling), data interpretation and development of vaccination and clinical therapeutic strategies to better communicate the benefits of HPV vaccination and lifestyle changes in cancer prevention, and approaches to take into account the preferences of Indigenous people in prevention and management of cancer driven by the Aboriginal community.

Ethical Approval

Ethics approval has been obtained from the University of Adelaide Human Research Ethics Committee (H-2016-246). Before being recruited, all participants will be required to sign an informed consent form, which includes consent for the authors to publish the findings in the peer-reviewed scientific literature. The authors confirm that supporting data and material in the study will be made available through Springer Nature's Data Support Services.

Study Population and Recruitment

We will recruit 1000 Aboriginal South Australian male and female adults, with a focus on Port Augusta, Whyalla, Port Lincoln, Mount Gambier, Ceduna, and Adelaide. Census data indicate approximately 22,000 Aboriginal adults reside in these areas. The investigators have a 13-year relationship with key Aboriginal stakeholder groups in these locations, who are willing and excited to be part of the study. Recruitment strategies will be based on those successfully implemented in the past, including the following: establishing service agreements with key Aboriginal community-controlled health organizations, liaising with community champions previously involved in our research, and encouraging word-of-mouth spread of knowledge.

Inclusion and Exclusion Criteria

Participants will be aged 18+ years, identify as being Aboriginal or Torres Strait Islander, and planning to live in South Australia for the next 3 years. Participants not enrolled during the original recruitment period will not be eligible to participate in the follow-up phases.

Collection of Human Papillomavirus and Oropharyngeal-Related Information

Permission to obtain sensitive information from participants will be sought, with relevant information related to alcohol and tobacco use, HPV diagnosis, health behaviors (including HPV vaccination status and sexual behaviors), and social determinants asked through a self-report questionnaire. Data will be collected by experienced Aboriginal research officers.

Collection of Utilities Information

We will design a questionnaire for the utility study, in which all 1000 participants taking part in the oral HPV prevalence study will be asked to indicate preferences (rank and utility scores) for 6 hypothetical states relating to oral HPV testing, precursor oropharyngeal cancer, and early-stage oropharyngeal cancer (including examinations and treatment). On the basis of standard methods used in the development of utilities, preferences for health states will be measured through ranking (1 through to 6), followed by a 2-stage standard gamble. We will focus on valuing the long-term oropharyngeal cancer health state of the average patient who survives up to 5 years after diagnosis and treatment, which is the most appropriate state for modeling cost-effectiveness of prophylactic HPV vaccination. We will seek to generate utility values for all cancer stages at diagnosis. The process for developing the health states will involve the following: (1) the most common stage(s) of HPV-associated oropharyngeal cancer at diagnosis identified from the literature; (2) the recommended treatment for the relevant stages(s) of oropharyngeal cancer identified and confirmed from published studies; and (3) the more common long-term consequences (applying to ≥50% patients) in patients surviving the initial treatment phase described based on the literature, and subsequent refinement by clinical experts involved in managing oropharyngeal cancer [52,53].

Collection of Oral Human Papillomavirus Data

All participants will be asked to provide a saliva sample using a commercially available kit (Omnigene 501; DNA Genotek Inc, Canada) from which microbial DNA for genotyping will be extracted. This involves the participant: (a) not eating or drinking for 30 min before collection; (b) spitting until 2 ml reaches the fill line on the container (takes 2-3 min); (c) closing the lid on the funnel (to release preservative liquid into tube); (d) removing the funnel lid on the container; and (e) placing the small cap on the tube and shaking the tube for 5 seconds. This results in over 100 µg of DNA collection, which is sufficient for the testing required. The sample can be kept at room temperature (for up to 12 months) until collection by the Aboriginal research assistants, who will send it to an appropriate laboratory for analysis. Saliva samples will be collected at baseline, 12 months, and 24 months.

Data Analysis

In brief, the analysis plan for each aim is described below.

Aim 1: To Yield Population Estimates of Oral Human Papillomavirus in the Aboriginal and Torres Strait Islander Population

DNA Extraction and Quality Check

Antonsson and colleagues have evaluated 3 different kits (all semi-automated) for DNA extraction, namely, Promega's Maxwell-16 Viral Total Nucleic Acid Purification Kit, QIAGEN's QIAamp Mini Elute Virus Spin Kit, and QIAamp Blood DNA Mini Kit (QIAcube). We will use the Promega Maxwell viral kit for DNA extraction as the DNA yield and quality was superior compared with the 2 other kits. β-globin polymerase chain reaction (PCR) with the primers PCO3 and PCO4 will be carried out on all samples to ensure that they contain enough cells to detect human DNA, and that no PCR inhibiting agents are present [54].

HPV Type Determination

We will analyze all samples with the optimized general primer (GP)+PCR system that detects most mucosal HPV types and all hrHPV types that have oncogenic potential in mucosal tissue

[54]. All HPV DNA positive samples will be sequenced to confirm viral DNA sequences. For the sequencing, HPV-positive PCR products will be purified with the Agencourt AMPure PCR purification kit in a magnetic 96-ring SPRIplate. Sequencing reactions containing the purified PCR products together with GP+primer and BigDye Terminator will be performed. Sequence reactions will be purified with the Agencourt CleanSEQ dye-terminator removal kit in a magnetic 96-ring SPRIplate. Direct sequencing will be carried out initially. Samples with multiple HPV types will be cloned before sequencing, with at least 5 clones sequenced per sample. Sequence reactions will be analyzed with an automated DNA sequencer (ABI model 3100). The DNA sequences will be compared with available sequences in GenBank through the BLAST server. We have chosen a standard PCR method, which has been used in several projects by Antonsson and proven to be both reliable and reproducible [4,55-57].

Specimen Variables

HPV status and genotypes found will be analyzed. The genotypes will also be divided into low-risk (not found in cancer; eg, HPV-6 and -11) and hrHPV types (found in cancer; eg, HPV-16 and -18). As multiple HPV infections are likely, incident infection will be defined as a new type-specific HPV infection not detected in a previous sample. We will determine the precision of HPV prevalence estimates obtainable with the sample of 1000 in age- and sex-specific subgroups. We will base these estimates on measurements in other populations by age and sex, and then characterize 95% CIs obtainable in the given sample size.

Aim 2: Using Preliminary Data From Aim 1, and Information on Prevalence of Other Risk Factors, to Estimate Burden of Human Papillomavirus-Related Oropharyngeal Cancer Among Aboriginal and Torres Strait Islander Australians

Sufficiently detailed information on oropharyngeal cancer rates overall, or the proportion of oropharyngeal cancers which are HPV-positive, are not available for the Indigenous population. Therefore, these rates will be estimated using published data on HPV-positive and HPV-negative oropharyngeal cancers in the general population [27,58]. Each estimate will be scaled to account for different risk factor prevalences. For HPV-positive cancers, we will use our preliminary findings on the relative prevalence of oral HPV in the Indigenous population compared with that in the general population [57] to scale rates of HPV-positive oropharyngeal cancer. Overall estimates of oropharyngeal cancer will be compared with available published data on the relative incidence of oropharyngeal cancer overall in the Indigenous versus the general population to ensure consistency [5].

Utilities and Costings

We will perform systematic reviews of utilities for oropharyngeal cancer diagnosis, surveillance, surgery, and the diagnosis/treatment of associated cancers. We will also perform systematic reviews of complication rates and associated utilities for surveillance and surgery. Aggregate costs for each step involved in screening, diagnosis, family counseling, referral and management pathways, and cancer diagnosis and treatment will be collated using methods previously employed by Canfell and colleagues for other cancer-related applications [59,60]. Briefly, detailed clinical pathways for current practice will be described using relevant patterns of care studies and clinical practice guidelines, and will take into account different patterns of care/attendance for treatment among Aboriginal and Torres Strait Islander Australians. Item costs of the component services will be obtained from the Medicare Benefit Schedule Online for outpatient medical services, the latest available National Hospital Cost Data Collection Round for inpatient services and the Pharmaceutical Benefits Schedule Online.

Aim 3: To Evaluate the Impact of Human Papillomavirus Vaccination as Currently Implemented on Oropharyngeal and Cervical Cancer Rates Among Aboriginal and Torres Strait Islander Australians

The results of Aim 2 will feed into an existing model of HPV transmission, vaccination, and natural history developed by Canfell and colleagues through previous grants from Australia's National Health and Medical Research Council (NHMRC). This model has been used extensively for evaluations around HPV and cervical cancer prevention in government-commissioned reports and in 20 journal publications. In the proposed study, this model will be further tailored to the Aboriginal and Torres Strait Islander population. The developed model will be used to make detailed predictions of the impact of HPV vaccination over time on oropharyngeal and cervical cancer among Aboriginal and Torres Strait Islander Australians, including under a range of age ranges for vaccination and dose/uptake assumptions. This will be based on the burden of HPV-attributable oropharyngeal and cervical cancer in the Indigenous population estimated in Aim 2, which will take into account different tobacco smoking prevalence or varied attributable fraction to allow for the higher proportion of HPV-negative tumors in the Indigenous population. Estimates of HPV vaccine uptake in Aboriginal and Torres Strait Islander Australians will be used, in conjunction with available data on HPV vaccine impact in Aboriginal and Torres Strait Islander populations or precursor/proxy outcomes, such as prevalence of infection with vaccine-included types and anogenital warts. We will validate model predictions against these previously reported outcomes [41,42].

Aim 4: To Evaluate Efficacy and Cost-Effectiveness of Targeted Extended Human Papillomavirus Vaccination on Oropharyngeal Cancer Among Aboriginal and Torres Strait Islanders, Incorporating the Effectiveness Against Both Cervical Cancer (in Females) and Oropharyngeal Cancer

We will use data from the literature review and utility estimations in Aim 2 to inform model assumptions on the demographics and risk profile of the population. To achieve higher coverage in this group, we will estimate impact and cost-effectiveness of funding extended catch-up vaccination for Aboriginal and Torres Strait Islander Australians (for those who did not receive the vaccine through the school-based program). A range of potential extended catch-up strategies will be considered, eg, funding HPV vaccination for females ± males

aged up to 18, 25, 30, or 45 years who have not already received a full course. We will consider both first and second generation HPV vaccines and also consider strategies involving revaccination of individuals who have already received the first generation vaccine with the second generation vaccine. We will also consider different potential delivery mechanisms, eg, via Aboriginal health services and/or other community providers. For each analysis, a large "virtual" sample of the Aboriginal and Torres Strait Islander population will be simulated. Each evaluation will then use all fitted parameter sets to derive a baseline result and 95% CI. These evaluations will simulate 10,000 individuals. All evaluations will be accompanied by extensive sensitivity analysis, using one-way and probabilistic sensitivity analysis techniques that will take into account the full range of identified fitted parameter sets. For each strategy, we will calculate a number of measures of effectiveness, including change in cancer incidence, mortality, life years saved, and quality-adjusted life years gained. We will also estimate absolute case numbers based on population projections available by age, sex, and calendar year for ASTI Australians. We will assess morbidity via calculation of quality-adjusted life years and calculate complication numbers from surveillance and surgery. We will take into account varying rates of attendance for treatment in the Indigenous population [61], but consider a range of assumptions in sensitivity analysis. We will provide detailed predictions of health resources utilization, including numbers of tests, biopsies, and treatments. We will assess costs of diagnosis, surveillance and cancer treatment, and the total budget impact for each year from 2017 to 2030. We will calculate incremental cost-effectiveness ratios for both life years saved and quality-adjusted life years. If results suggest that extended HPV vaccination among Aboriginal and Torres Strait Islander Australians is not cost-effective at any age threshold, we will perform threshold analysis to determine the cost at which extended HPV vaccination to different upper age thresholds becomes cost-effective.

Ethical Approval

Ethical approval for this study has been obtained by the University of Adelaide Human Research Ethics Committee (H-2016-246).

Results

Participant recruitment for this study commenced in February 2018 and enrollment is ongoing. The first results are expected to be submitted for publication in 2019.

Discussion

Study Overview

Oropharyngeal cancer is an important cancer affecting Aboriginal and Torres Strait Islander Australians at a higher rate than other Australians. Infection with hrHPV is a significant risk factor for oropharyngeal cancer. HPV vaccination is effective against the 2 most common types of hrHPV, with some promise that current vaccines may prevent oral infections (potentially reducing the risk of oropharyngeal cancer). Given the elevated risk of HPV-related cancers in this group, it may be reasonable to extend the comparatively brief timeframe (when aged 12-13 years) in which Aboriginal and Torres Strait Islander Australians can access an otherwise costly vaccine via public funding. The project will have a number of important outcomes. Synthesis of evidence will directly support estimates of the burden of oropharyngeal cancer among Aboriginal and Torres Strait Islander Australians and the effectiveness and cost-effectiveness of prevention. This will be important for health services planning, and for Aboriginal health worker and patient education. The project provides a key example of how carefully calibrated, data-driven disease models can integrate with Aboriginal community views and expectations to estimate disease burden and to guide policy decisions.

Study Strengths

The strengths of the study include it being the first to obtain and link all the information on cervical and oropharyngeal cancers via modeling (possibly in any population but certainly for the Australian Aboriginal and Torres Strait Islander population) and the focus on engagement, enabling community and individual preferences to play a large role in decision making for Aboriginal and Torres Strait Islander Australians. Burger and colleagues investigated the impact of HPV on 6 HPV-associated cancers, including cervical and oropharyngeal cancer, among 5 ethnic groups in the United States, one of which included Native American/Alaskan Natives [62].

Study Limitations

The limitations include the sample frame for oral HPV prevalence assessment being pragmatic, ie, utilizing convenience sampling methodology rather than attempting to be representative. Although there is a risk of sampling bias, the efforts required to obtain a representative sample are recognized as being both expensive and time-consuming [63]. Additionally, it is recognized that oral HPV measurement through saliva sampling is blunt as it does not provide a direct measure of HPV exposure at each potential cancer site. Finally, as in any modeled assessment, assumptions about future vaccination and screening coverage need to be made, but we remain committed to engaging the Aboriginal and Torres Strait Islander community in consultation about such assumptions via the study's Aboriginal Reference Group.

Acknowledgments

This study is governed by an Aboriginal Reference Group, who will oversee the orchestration, delivery, and feedback of the study findings as it relates to the health and well-being of Aboriginal and Torres Strait Islander Australians. The authors sincerely

acknowledge and appreciate all that this Reference Group does. Funding is from a NHMRC project grant (APP1120215). LJ, GG and AA are all supported by NHMRC research fellowships (APP1102587, APP1105399 and APP1065293, respectively).

Authors' Contributions

All authors are named investigators on the project; they all contributed to the intellectual input of the study design and in writing this protocol.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Peer Review Assessment from Australia's National Health & Medical Research Council

[PDF File (Adobe PDF File), 279KB-Multimedia Appendix 1]

References

1. Australian Government Department of Health. 2016. 4.6 Human papillomavirus URL: http://www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/Handbook10-home~handbook10part4~handbook10-4-6[WebCite Cache ID 6yjsOZLem]
2. Marur S, D'Souza G, Westra WH, Forastiere AA. HPV-associated head and neck cancer: a virus-related cancer epidemic. Lancet Oncol 2010 Aug;11(8):781-789 [FREE Full text] [doi: 10.1016/S1470-2045(10)70017-6] [Medline: 20451455]
3. Communicable Diseases Network Australia. Human Papillomavirus Surveillance Plan – an integrated approach to monitoring the impact of HPV vaccine in Australia URL: http://www.health.gov.au/internet/main/publishing.nsf/Content/E5B543CE209E55C3CA257F48001D65EF/$File/HPV-Surveillance-Plan.pdf[WebCite Cache ID 6yjsVPxJ0]
4. Antonsson A, Cornford M, Perry S, Davis M, Dunne MP, Whiteman DC. Prevalence and risk factors for oral HPV infection in young Australians. PLoS One 2014;9(3):e91761 [FREE Full text] [doi: 10.1371/journal.pone.0091761] [Medline: 24637512]
5. Cramb S. Cancer Council Queensland (Australia). 1997. Head and neck cancers among Indigenous Australians living in Queensland,- URL: https://static1.squarespace.com/static/575e13942b8ddeb3fba54b8a/t/57e878bdbebafba41130b682/1474853134375/WICC_Handbook_A4_TTT+Update_V16_NEW.pdf[WebCite Cache ID 6yjsawmaA]
6. Globocan. Cervical cancer estimated incidence, mortality and prevalence worldwide in 2012 URL: http://globocan.iarc.fr/old/FactSheets/cancers/cervix-new.asp [accessed 2018-04-17] [WebCite Cache ID 6yjsdSp48]
7. Walboomers JM, Jacobs MV, Manos MM, Bosch FX, Kummer JA, Shah KV, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. J Pathol 1999 Sep;189(1):12-19. [doi: 10.1002/(SICI)1096-9896(199909)189:1<12::AID-PATH431>3.0.CO;2-F] [Medline: 10451482]
8. Moore SP, Antoni S, Colquhoun A, Healy B, Ellison-Loschmann L, Potter JD, et al. Cancer incidence in indigenous people in Australia, New Zealand, Canada, and the USA: a comparative population-based study. Lancet Oncol 2015 Nov;16(15):1483-1492. [doi: 10.1016/S1470-2045(15)00232-6] [Medline: 26476758]
9. Australian Institute of Health and Welfare and Cancer Australia. Cancer in Aboriginal and Torres Strait Islander peoples of Australia: an overview URL: https://www.aihw.gov.au/reports/cancer/cancer-in-indigenous-australians-overview/contents/table-of-contents[WebCite Cache ID 6yjsgUjBx]
10. Gupta B, Johnson NW, Kumar N. Global epidemiology of head and neck cancers: a continuing challenge. Oncology 2016;91(1):13-23. [doi: 10.1159/000446117] [Medline: 27245686]
11. Ariyawardana A, Johnson NW. Trends of lip, oral cavity and oropharyngeal cancers in Australia 1982-2008: overall good news but with rising rates in the oropharynx. BMC Cancer 2013 Jul 06;13:333 [FREE Full text] [doi: 10.1186/1471-2407-13-333] [Medline: 23829309]
12. Radoï L, Luce D. A review of risk factors for oral cavity cancer: the importance of a standardized case definition. Community Dent Oral Epidemiol 2013 Apr;41(2):97-109. [doi: 10.1111/j.1600-0528.2012.00710.x] [Medline: 22882534]
13. Friborg JT, Yuan JM, Wang R, Koh WP, Lee HP, Yu MC. A prospective study of tobacco and alcohol use as risk factors for pharyngeal carcinomas in Singapore Chinese. Cancer 2007 Mar 15;109(6):1183-1191 [FREE Full text] [doi: 10.1002/cncr.22501] [Medline: 17315158]
14. Perera M, Al-Hebshi NN, Perera I, Ipe D, Ulett GC, Speicher DJ, et al. A dysbiotic mycobiome dominated byis identified within oral squamous-cell carcinomas. J Oral Microbiol 2017 Oct;9(1):1385369 [FREE Full text] [doi: 10.1080/20002297.2017.1385369] [Medline: 29152157]
15. Al-Hebshi NN, Nasher AT, Maryoud MY, Homeida HE, Chen T, Idris AM, et al. Inflammatory bacteriome featuring Fusobacterium nucleatum and Pseudomonas aeruginosa identified in association with oral squamous cell carcinoma. Sci Rep 2017 May 12;7(1):1834 [FREE Full text] [doi: 10.1038/s41598-017-02079-3] [Medline: 28500338]

16. Lubek JE, Clayman L. An update on squamous carcinoma of the oral cavity, oropharynx, and maxillary sinus. Oral Maxillofac Surg Clin North Am 2012 May;24(2):307-316 [FREE Full text] [doi: 10.1016/j.coms.2012.01.003] [Medline: 22341511]
17. National Cancer Institute. Oral Cavity and Pharynx Cancer URL: https://seer.cancer.gov/archive/csr/1975_2012/[WebCite Cache ID 6vjsluw6B]
18. Sudhoff HH, Schwarze HP, Winder D, Steinstraesser L, Görner M, Stanley M, et al. Evidence for a causal association for HPV in head and neck cancers. Eur Arch Otorhinolaryngol 2011 Nov;268(11):1541-1547. [doi: 10.1007/s00405-011-1714-8] [Medline: 21792686]
19. Schnelle C, Whiteman DC, Porceddu SV, Panizza BJ, Antonsson A. Past sexual behaviors and risks of oropharyngeal squamous cell carcinoma: a case-case comparison. Int J Cancer 2017 Mar 01;140(5):1027-1034 [FREE Full text] [doi: 10.1002/ijc.30519] [Medline: 27859177]
20. Gillison ML, Broutian T, Pickard RK, Tong ZY, Xiao W, Kahle L, et al. Prevalence of oral HPV infection in the United States, 2009-2010. J Am Med Assoc 2012 Feb 15;307(7):693-703 [FREE Full text] [doi: 10.1001/jama.2012.101] [Medline: 22282321]
21. Mehanna H, Beech T, Nicholson T, El-Hariry I, McConkey C, Paleri V, et al. Prevalence of human papillomavirus in oropharyngeal and nonoropharyngeal head and neck cancer--systematic review and meta-analysis of trends by time and region. Head Neck 2013 May;35(5):747-755. [doi: 10.1002/hed.22015] [Medline: 22267298]
22. Hong A, Zhang X, Jones D, Veillard AS, Zhang M, Martin A, et al. Relationships between p53 mutation, HPV status and outcome in oropharyngeal squamous cell carcinoma. Radiother Oncol 2016 Feb;118(2):342-349. [doi: 10.1016/j.radonc.2016.02.009] [Medline: 26952933]
23. Gillison ML, D'Souza G, Westra W, Sugar E, Xiao W, Begum S, et al. Distinct risk factor profiles for human papillomavirus type 16-positive and human papillomavirus type 16-negative head and neck cancers. J Natl Cancer Inst 2008 Mar 19;100(6):407-420. [doi: 10.1093/jnci/djn025] [Medline: 18334711]
24. Zhao L, Wang L, Ji W, Wang X, Zhu X, Feng Q, et al. Association between plasma angiotensin-converting enzyme level and radiation pneumonitis. Cytokine 2007 Jan;37(1):71-75. [doi: 10.1016/j.cyto.2007.02.019] [Medline: 17408964]
25. Fang F, Tsai WL, Chien CY, Chiu HC, Wang CJ, Chen HC, et al. Changing quality of life in patients with advanced head and neck cancer after primary radiotherapy or chemoradiation. Oncology 2005 Aug;68(4-6):405-413. [doi: 10.1159/000086982] [Medline: 16020970]
26. Curran D, Giralt J, Harari PM, Ang KK, Cohen RB, Kies MS, et al. Quality of life in head and neck cancer patients after treatment with high-dose radiotherapy alone or in combination with cetuximab. J Clin Oncol 2007 Jun 01;25(16):2191-2197. [doi: 10.1200/JCO.2006.08.8005] [Medline: 17538164]
27. Hong A, Lee CS, Jones D, Veillard AS, Zhang M, Zhang X, et al. Rising prevalence of human papillomavirus-related oropharyngeal cancer in Australia over the last 2 decades. Head Neck 2016 May;38(5):743-750. [doi: 10.1002/hed.23942] [Medline: 25521312]
28. SA Health. Aboriginal and Torres Strait Islander Companion Document to the State-Wide Cancer Control Plan (2011-2015) URL: http://www.sahealth.sa.gov.au/wps/wcm/connect/public+content/sa+health+internet/clinical+resources/clinical+topics/cancer+and+oncology/state-wide+cancer+control+plan+2011+2015[WebCite Cache ID 6vjssw8Bc]
29. The Lowitja Institute. Brisbane: School of Population Health, The University of Queensland; 2007. The burden of disease and injury in Aboriginal and Torres Strait Islander peoples 2003 URL: https://www.lowitja.org.au/sites/default/files/docs/Indigenous-BoD-Report.pdf[WebCite Cache ID 6vjswAQxx]
30. Cancer Council Australia. National Cancer Prevention Policy 2007-09 URL: https://www.cancer.org.au/content/pdf/CancerControlPolicy/NationalCancerPreventionPolicy/NCPP07-09-FULL.pdf[WebCite Cache ID 6vjsxGrDI]
31. Australian Bureau of Statistics. Australian Aboriginal Torres Strait Islander Health Survey: first results, Australia, 2012-13 URL: http://www.abs.gov.au/ausstats/abs@.nsf/mf/4727.0.55.001[WebCite Cache ID 6vjsyLRon]
32. Cleveland JL, Junger ML, Saraiya M, Markowitz LE, Dunne EF, Epstein JB. The connection between human papillomavirus and oropharyngeal squamous cell carcinomas in the United States: implications for dentistry. J Am Dent Assoc 2011 Aug;142(8):915-924. [Medline: 21804058]
33. Skinner SR, Szarewski A, Romanowski B, Garland SM, Lazcano-Ponce E, Salmerón J, VIVIANE Study Group. Efficacy, safety, and immunogenicity of the human papillomavirus 16/18 AS04-adjuvanted vaccine in women older than 25 years: 4-year interim follow-up of the phase 3, double-blind, randomised controlled VIVIANE study. Lancet 2014 Dec 20;384(9961):2213-2227. [doi: 10.1016/S0140-6736(14)60920-X] [Medline: 25189358]
34. Gertig DM, Brotherton JM, Saville M. Measuring human papillomavirus (HPV) vaccination coverage and the role of the National HPV Vaccination Program Register, Australia. Sex Health 2011 Jun;8(2):171-178. [doi: 10.1071/SH10001] [Medline: 21592430]
35. Bonanni P, Boccalini S, Bechini A. Efficacy, duration of immunity and cross protection after HPV vaccination: a review of the evidence. Vaccine 2009 May 29;27(Suppl 1):A46-A53. [doi: 10.1016/j.vaccine.2008.10.085] [Medline: 19480962]
36. Schiller JT, Müller M. Next generation prophylactic human papillomavirus vaccines. Lancet Oncol 2015 May;16(5):e217-e225. [doi: 10.1016/S1470-2045(14)71179-9] [Medline: 25943066]

37. Herrero R, Quint W, Hildesheim A, Gonzalez P, Struijk L, Katki HA, CVT Vaccine Group. Reduced prevalence of oral human papillomavirus (HPV) 4 years after bivalent HPV vaccination in a randomized clinical trial in Costa Rica. PLoS One 2013 Jul;8(7):e68329 [FREE Full text] [doi: 10.1371/journal.pone.0068329] [Medline: 23873171]
38. Beachler DC, Kreimer AR, Schiffman M, Herrero R, Wacholder S, Rodriguez AC, Costa Rica HPV Vaccine Trial (CVT) Group. Multisite HPV16/18 vaccine efficacy against cervical, anal, and oral HPV infection. J Natl Cancer Inst 2016 Jan;108(1) [FREE Full text] [doi: 10.1093/jnci/djv302] [Medline: 26467666]
39. Brotherton JML, Murray SL, Hall MA, Andrewartha LK, Banks CA, Meijer D, et al. Human papillomavirus vaccine coverage among female Australian adolescents: success of the school-based approach. Med J Aust 2013 Nov 04;199(9):614-617. [Medline: 24182228]
40. Smith MA, Liu B, McIntyre P, Menzies R, Dey A, Canfell K. Fall in genital warts diagnoses in the general and Indigenous Australian population following implementation of a national human papillomavirus vaccination program: analysis of routinely collected national hospital data. J Infect Dis 2015 Jan 01;211(1):91-99. [doi: 10.1093/infdis/jiu370] [Medline: 25117753]
41. Ali H, McManus H, O'Connor CC, Callander D, Kong M, Graham S, et al. Human papillomavirus vaccination and genital warts in young Indigenous Australians: national sentinel surveillance data. Med J Aust 2017 Mar 20;206(5):204-209. [Medline: 28301790]
42. Angus S. Cancer Forum. 2005. A model for engaging and empowering indigenous women in cancer screening URL: https://cancerforum.org.au/wp-content/uploads/2015/06/CF05Mar_13-17.pdf[WebCite Cache ID 6vjt7FNst]
43. Barbaro B, Brotherton JM. Assessing HPV vaccine coverage in Australia by geography and socioeconomic status: are we protecting those most at risk? Aust N Z J Public Health 2014 Oct;38(5):419-423. [doi: 10.1111/1753-6405.12218] [Medline: 24962721]
44. Wheeler CM, Skinner SR, Del Rosario-Raymundo MR, Garland SM, Chatterjee A, Lazcano-Ponce E, VIVIANE Study Group. Efficacy, safety, and immunogenicity of the human papillomavirus 16/18 AS04-adjuvanted vaccine in women older than 25 years: 7-year follow-up of the phase 3, double-blind, randomised controlled VIVIANE study. Lancet Infect Dis 2016 Oct;16(10):1154-1168. [doi: 10.1016/S1473-3099(16)30120-7] [Medline: 27373900]
45. Mazza D, Petrovic K, Chakraborty S. HPV vaccination of adult women: an audit of Australian general practitioners. Aust N Z J Obstet Gynaecol 2012 Dec;52(6):528-533. [doi: 10.1111/ajo.12002] [Medline: 23046059]
46. Kulasingam S, Connelly L, Conway E, Hocking JS, Myers E, Regan DG, et al. A cost-effectiveness analysis of adding a human papillomavirus vaccine to the Australian National Cervical Cancer Screening Program. Sex Health 2007 Sep;4(3):165-175. [Medline: 17931529]
47. Smith MA, Lew JB, Walker RJ, Brotherton JM, Nickson C, Canfell K. The predicted impact of HPV vaccination on male infections and male HPV-related cancers in Australia. Vaccine 2011 Nov 08;29(48):9112-9122. [doi: 10.1016/j.vaccine.2011.02.091] [Medline: 21419773]
48. Simms KT, Smith MA, Lew JB, Kitchener HC, Castle PE, Canfell K. Will cervical screening remain cost-effective in women offered the next generation nonavalent HPV vaccine? Results for four developed countries. Int J Cancer 2016 Dec 15;139(12):2771-2780 [FREE Full text] [doi: 10.1002/ijc.30392] [Medline: 27541596]
49. Howard K, Salkeld G, McCaffery K, Irwig L. HPV triage testing or repeat Pap smear for the management of atypical squamous cells (ASCUS) on Pap smear: is there evidence of process utility? Health Econ 2008 May;17(5):593-605. [doi: 10.1002/hec.1278] [Medline: 17764095]
50. Myers E, Green S, Lipkus I. Patient preferences for health states related to HPV infection: visual analog scales vs time trade-off elicitation. 2004 Jun 12 Presented at: Proceedings of 21st International Papillomavirus Conference; 2004; Mexico City.
51. Woodhall SC, Jit M, Soldan K, Kinghorn G, Gilson R, Nathan M, QOLIGEN study group. The impact of genital warts: loss of quality of life and cost of treatment in eight sexual health clinics in the UK. Sex Transm Infect 2011 Oct;87(6):458-463 [FREE Full text] [doi: 10.1136/sextrans-2011-050073] [Medline: 21636616]
52. Simonella L, Canfell K. Development of a quality framework for models of cervical screening and its application to evaluations of the cost-effectiveness of HPV vaccination in developed countries. Vaccine 2015 Jan 01;33(1):34-51. [doi: 10.1016/j.vaccine.2014.08.048] [Medline: 25171843]
53. Simonella L, Howard K, Canfell K. A survey of population-based utility scores for cervical cancer prevention. BMC Res Notes 2014 Dec 11;7:899 [FREE Full text] [doi: 10.1186/1756-0500-7-899] [Medline: 25495005]
54. de Roda Husman AM, Walboomers JM, Hopman E, Bleker OP, Helmerhorst TM, Rozendaal L, et al. HPV prevalence in cytomorphologically normal cervical scrapes of pregnant women as determined by PCR: the age-related pattern. J Med Virol 1995 Jun;46(2):97-102. [doi: 10.1002/jmv.1890460203]
55. Hansson BG, Rosenquist K, Antonsson A, Wennerberg J, Schildt EB, Bladström A, et al. Strong association between infection with human papillomavirus and oral and oropharyngeal squamous cell carcinoma: a population-based case-control study in southern Sweden. Acta Otolaryngol 2005 Dec;125(12):1337-1344. [doi: 10.1080/00016480510043945] [Medline: 16303684]

56. Antonsson A, Nancarrow DJ, Brown IS, Green AC, Drew PA, Watson DI, Australian Cancer Study. High-risk human papillomavirus in esophageal squamous cell carcinoma. Cancer Epidemiol Biomarkers Prev 2010 Aug;19(8):2080-2087 [FREE Full text] [doi: 10.1158/1055-9965.EPI-10-0033] [Medline: 20696664]
57. Antonsson A, Neale RE, Boros S, Lampe G, Coman WB, Pryor DI, et al. Human papillomavirus status and p16(INK4A) expression in patients with mucosal squamous cell carcinoma of the head and neck in Queensland, Australia. Cancer Epidemiol 2015 Apr;39(2):174-181. [doi: 10.1016/j.canep.2015.01.010] [Medline: 25677091]
58. Hocking JS, Stein A, Conway EL, Regan D, Grulich A, Law M, et al. Head and neck cancer in Australia between 1982 and 2005 show increasing incidence of potentially HPV-associated oropharyngeal cancers. Br J Cancer 2011 Mar 01;104(5):886-891 [FREE Full text] [doi: 10.1038/sj.bjc.6606091] [Medline: 21285981]
59. Medical Service Advisory Committee (MSAC). 2013. MSAC Application No. 1276. National Cervical Screening Program Renewal: Effectiveness modelling and economic evaluation in the Australian setting URL: http://www.health.gov.au/internet/msac/publishing.nsf/Content/1276-public[WebCite Cache ID 6yjtHP5Yf]
60. Lew J, Howard K, Gertig D, Smith M, Clements M, Nickson C, et al. Expenditure and resource utilisation for cervical screening in Australia. BMC Health Serv Res 2012 Dec 05;12:446 [FREE Full text] [doi: 10.1186/1472-6963-12-446] [Medline: 23216968]
61. Moore SP, Green AC, Bray F, Garvey G, Coory M, Martin J, et al. Survival disparities in Australia: an analysis of patterns of care and comorbidities among indigenous and non-indigenous cancer patients. BMC Cancer 2014 Jul 18;14:517 [FREE Full text] [doi: 10.1186/1471-2407-14-517] [Medline: 25037075]
62. Burger EA, Lee K, Saraiya M, Thompson TD, Chesson HW, Markowitz LE, et al. Racial and ethnic disparities in human papillomavirus-associated cancer burden with first-generation and second-generation human papillomavirus vaccines. Cancer 2016 Dec 01;122(13):2057-2066 [FREE Full text] [doi: 10.1002/cncr.30007] [Medline: 27124396]
63. Australian Bureau of Statistics. National Aboriginal Torres Strait Islander Social Survey, 2014-15 URL: http://www.abs.gov.au/ausstats/abs@.nsf/mf/4714.0[WebCite Cache ID 6yjtLYoCr]

Abbreviations

GP: general primers
HPV: human papillomavirus
hrHPV: high-risk human papillomavirus
NHMRC: National Health and Medical Research Council
NHVP: National HPV Vaccination Program
PCO3: (5'CTTCTGACACAACTGTGTTCACTAGC3') oligonucleotide
PCO4: (5'TCACCACAACTTCATCCACGTTCACC3') oligonucleotide
PCR: polymerase chain reaction

Edited by G Eysenbach; submitted 25.03.18; peer-reviewed by C Schnelle; comments to author 31.03.18; revised version received 03.04.18; accepted 04.04.18; published 08.06.18

Please cite as:
Jamieson L, Garvey G, Hedges J, Mitchell A, Dunbar T, Leane C, Hill I, Warren K, Brown A, Ju X, Roder D, Logan R, Johnson N, Smith M, Antonsson A, Canfell K
Human Papillomavirus and Oropharyngeal Cancer Among Indigenous Australians: Protocol for a Prevalence Study of Oral-Related Human Papillomavirus and Cost-Effectiveness of Prevention
JMIR Res Protoc 2018;7(6):e10503
URL: http://www.researchprotocols.org/2018/6/e10503/
doi: 10.2196/10503
PMID: 29884604

13.4 Appendix D: Published baseline findings of the HPV-OPC project

JAMA Network Open

Original Investigation | Infectious Diseases

Prevalence of Oral Human Papillomavirus Infection Among Australian Indigenous Adults

Lisa M. Jamieson, PhD; Annika Antonsson, PhD; Gail Garvey, PhD; Xiangqun Ju, PhD; Megan Smith, PhD; Richard M. Logan, PhD; Newell W. Johnson, PhD; Joanne Hedges, MPH; Sneha Sethi, MDS; Terry Dunbar, PhD; Cathy Leane, MPH; Isaac Hill, MPH; Alex Brown, PhD; David Roder, PhD; Marjorie De Souza, PhD; Karen Canfell, DPhil

Abstract

IMPORTANCE Human papillomavirus (HPV) infection is associated with oropharyngeal squamous cell carcinoma. International estimates suggest overall oral HPV prevalence is 7.5%, with prevalence of oral HPV types 16 and 18 being 1.6%; prior Australian estimates suggest oral HPV prevalence is 2.3%, with HPV-16 and HPV-18 being 1.3%.

OBJECTIVES To estimate the prevalence of oral HPV infection among Indigenous Australians and to report the prevalence of factors associated with high-risk HPV types (ie, HPV-16 and HPV-18) and HPV types linked with Heck disease (ie, HPV-13 and HPV-32).

DESIGN, SETTING, AND PARTICIPANTS This cross-sectional study analyzed HPV screening results from saliva samples collected from 1011 Indigenous Australians between February 2018 and January 2019. Data were analyzed from May 2018 to May 2019. Recruitment occurred through Aboriginal Community Controlled Health Organisations in South Australia. Eligibility included identifying as Indigenous, residing in South Australia, and being aged 18 years or older.

MAIN OUTCOMES AND MEASURES Saliva samples were collected, with microbial DNA for genotyping extracted. Sociodemographic parameters, health-related behaviors, and sexual history data were collected. Analyses were stratified by sex as well as by HPV types 13 and 32 (Heck disease) and 16 and 18 (high risk of oropharyngeal squamous cell carcinoma). Multivariable analyses were conducted to obtain adjusted odds ratios (ORs).

RESULTS Data were obtained for 910 participants (median [interquartile range] age, 37 [27-51] years); 595 participants (65%) were female and 572 (63%) resided in nonmetropolitan locations. In all, 321 saliva samples (35.3%; 95% CI, 32.2%-38.4%) were positive for oral HPV (106 [33.7%] men; 215 [36.1%] women). The highest prevalence was found for HPV types 13 and 32 (207 [22.7%] total; 60 [19.0%] men; 147 [24.7%] women) followed by HPV types 16 and 18 (30 [3.3%] total; 9 [2.9%] men; 21 [3.5%] women). After multivariable analysis, risk factors associated with HPV types 13 and 32 included nonmetropolitan residential status (OR, 2.06; 95% CI, 1.10-3.88) and not having had a tonsillectomy (OR, 2.74; 95% CI, 1.05-7.16). Among women, having obtained a high school education or less was associated with lower odds of HPV-16 and HPV-18 infection (OR, 0.16; 95% CI, 0.03-0.97).

CONCLUSIONS AND RELEVANCE Prevalence of oral HPV infection in a large sample of Indigenous Australians was high, with one-third testing positive. The most prevalent HPV types were those associated with Heck disease. The prevalence of HPV types associated with oropharyngeal squamous cell carcinoma exceeded both Australian and international population-level estimates.

JAMA Network Open. 2020;3(6):e204951. doi:10.1001/jamanetworkopen.2020.4951

Key Points

Question What is the prevalence of oral human papillomavirus (HPV) infection among Indigenous Australians, a group at risk of oropharyngeal squamous cell carcinoma?

Findings This cross-sectional study examined 910 Indigenous Australians for HPV infection with a particular focus on high-risk HPV types. Thirty-five percent of study participants had an oral HPV infection, 15 times the incidence reported in a study of young Australians and 5 times that reported in a systematic review from other countries.

Meaning The findings of this study indicate that Indigenous Australians may be at higher risk of developing HPV-related oral cancer, which suggests that increased HPV vaccination coverage among this vulnerable population may be beneficial.

Author affiliations and article information are listed at the end of this article.

Introduction

Oropharyngeal squamous cell carcinoma (OPSCC) associated with human papillomavirus (HPV) disproportionately affects men and has one of the most rapidly increasing incidences of any cancer in high-income countries.[1] The increased incidence is particularly noted among younger cohorts with minimal exposure to smoking and alcohol, the risk factors most commonly associated with OPSCC; the increased HPV incidence may be attributable to oral exposure to infected anogenital sites with changing sexual behaviors.[2,3] Globally, the proportion of OPSCC attributable to HPV has been estimated as 23% to 31%; however, this varies by setting, particularly regarding exposure to HPV, tobacco, and alcohol.[4,5] In Australia, Hong et al[3] reported a more than 3-fold increase in the percentage of HPV-positive OPSCC in the last 2 decades, from 20% to 63%; HPV-16 is the most common type in HPV-positive OPSCC, although HPV-18 also plays a role.[6] The 2 types together account for 85% of HPV-positive OPSCC (83% HPV-16; 2% HPV-18).[5] In 2012, the incidence of OPSCC in men overtook that of cervical cancer in women in the United States,[7] and similar findings were observed in the United Kingdom in 2016.[8] Australian OPSCC incidence trends are in line with other high-income countries.[3] While these countries have also experienced reduced rates of cervical cancer due to successful screening initiatives, the increase in OPSCC remains notable.

Focal epithelial hyperplasia, or Heck disease, is a relatively benign and rare condition caused by oral HPV types 13 or 32.[9-12] It was first identified among a Navajo population in the United States[13] and has since been reported among other indigenous groups throughout the world.[14,15] Heck disease is characterized by multiple white or pink papules that occur diffusely throughout the oral cavity, with morphology that can present as slightly pale, smooth, or roughened surfaces. Although the papules will spontaneously regress without treatment over time, some patients opt for excisional biopsy for functional or cosmetic purposes.[16]

Aboriginal and Torres Strait Islanders (hereafter respectfully termed *Indigenous*) are the first peoples of Australia, having resided in the country for more than 50 000 years. Contemporary Indigenous Australians represent 3.3% of the total Australian population.[17] They are overrepresented in almost all cancer statistics, including cancers of the head and neck.[18] In an analysis of cancer registry data, Banham et al[19] reported that in comparison with the general population of Australia, Indigenous individuals were 10 years younger at diagnosis, to be residents of geographically remote locations, and to have primary cancer sites of the head and neck, lung, liver, and cervix. In 2009 to 2013, Indigenous Australians were 1.9 times more likely to be diagnosed with head and neck cancer than non–Indigenous Australians, and were 3.4 times more likely to die.[20] Risk of cancer death was associated with advanced stage at first observation, with more Indigenous than non-Indigenous individuals having distant metastases at diagnosis. Although HPV vaccine coverage across Indigenous adolescents in Australia is high, course completion is generally lower.[21] Evidence suggests that while HPV infection in other anatomical sites is similar to non–Indigenous Australians, Indigenous Australians experience a higher prevalence of risk factors and other HPV genotypes.[22]

In a systematic review of 9 studies that collected oral HPV data from 3762 cancer-free, HIV-negative individuals from the United States, Brazil, Mexico, and Finland, Wood et al[23] reported that 7.5% (95% CI, 6.7%-8.4%) had an oral infection with any HPV type at baseline. In a study involving 307 Australian university students (aged 18-35 years), 7 students (6 men and 1 woman; 2.3%; 95% CI, 0.6%-3.9%) tested positive for oral HPV infection. Those positive for oral HPV were more likely to have received oral sex from more partners in their lifetime.[24]

Given the high risk of Indigenous Australians having both oral HPV infection and OPSCC and the potential benefits of HPV vaccination, the aims of this study were as follows: (1) to estimate the prevalence of oral HPV infection among Indigenous Australians; (2) to identify risk factors associated with Heck disease HPV types (HPV-13 and HPV-32); and (3) to identify risk factors associated with OPSCC-related HPV types (HPV-16 and HPV-18). We hypothesized that levels of any oral HPV infection, oral HPV infection associated with Heck disease (HPV-13 and HPV-32), and oral HPV infection associated with OPSCC (HPV-16 and HPV-18) among an Indigenous adult population would

be higher than overall population estimates. We additionally hypothesized that risk factors for oral HPV infection would include male sex, social disadvantage, tobacco use, and early and frequent sexual activity.

Methods

Study Design and Participants

We used a large convenience sample (n = 1011) of adults aged 18 years or older who identified as being Indigenous in the Australian state of South Australia. Data were collected between February 2018 and January 2019 as part of a broader study investigating HPV and OPSCC among Indigenous Australians[25] and were analyzed from October 2018 to July 2019. The study was governed by an Indigenous Reference Group, with data collected by trained Indigenous research officers. Participants were primarily recruited through Aboriginal Community Controlled Health Organisations, which were key stakeholders in the study. After having the study explained and signing informed consent forms, participants were asked to complete a questionnaire (with assistance from study staff if requested) that contained information on sociodemographic characteristics, health-related behaviors including tobacco and alcohol use, and sexual history. Participants then provided a saliva sample through spitting and dribbling that was collected in a commercially available kit (DNA Genotek Inc), from which microbial DNA was extracted for genotyping.

Ethical approval was received from the University of Adelaide Human Research Ethics Committee and the Aboriginal Health Council of South Australia's Human Research Ethics Committee. This study follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cross-sectional studies.

Self-reported Data

Sociodemographic characteristics included age, sex, geographic location, education, income, ownership of a means-tested government health care card, number of people in house the previous night, and car ownership. Health-related behaviors surveyed included tobacco, alcohol, nonprescription tobacco substitute (ie, vaporizer or e-cigarette), recreational drug use, having ever been diagnosed with an HPV infection (self-reported), HPV vaccination status (self-reported) and having had a tonsillectomy. Sexual behaviors across lifetime included number of people passionately kissed, having ever given oral sex, having ever received oral sex, having experienced sexual intercourse, and current relationship status. Age was dichotomized based on a median split. Geographic location was defined as metropolitan (ie, residing in Adelaide, South Australia's capital city) and nonmetropolitan (residing elsewhere in the state). Highest educational attainment was categorized as high school or less and trade, TAFE, or university (TAFE stands for technical and further education and provides training for vocational occupations). Income was defined as job or Centrelink or other (Centrelink is the government agency responsible for means-tested welfare payments). Similarly, enrollment in government-administered health care card is means tested, and enables access to services such as publicly funded dental care. Number of people in house the previous night was used as a proxy measure of socioeconomic status (as used in studies conducted by the Australian Institute of Health and Welfare[26]) and was categorized according to whether the total number of people spending the previous night in the participant's residence was 4 or more or less than 4. Tobacco smoking status was defined as currently smoking tobacco, formerly smoked, and never smoked, while response categories for alcohol consumption included daily, weekly, monthly, or never.

Laboratory Analysis

A viral kit for DNA extraction (Promega Maxwell) was used. β-globin polymerase chain reaction (PCR) with the primers PCO3 and PCO4 was carried out on all samples to ensure the presence of human

DNA and that no PCR-inhibiting agents were present.[27] All samples were analyzed with a nested PCR system (MY09/11) and $GP^{5+/6+}$ that detects most mucosal HPV types and all high-risk HPV types that have oncogenic potential in mucosal tissue.[28,29] All HPV-positive DNA samples were sequenced to confirm viral DNA sequences. For sequencing, HPV-positive PCR products were purified with a PCR purification kit in a magnetic 96-ring SPRIplate (Agencourt Biosciences). Sequencing reactions were performed containing the purified PCR products together with GP^{+} primer and BigDye Terminator. Sequence reactions were purified with a dye-terminator removal kit (Agencourt Biosciences) in a magnetic 96-ring SPRIplate. Direct sequencing was conducted, and sequence reactions were analyzed with an automated DNA sequencer (Applied Biosystems). The DNA sequences were compared with available sequences in GenBank through the National Center for Biotechnology Information BLASTn suite server.[30] Participants with β-globin–positive saliva samples were included in the data analysis. (β-globin is a DNA integrity check; any samples with negative β-globin were invalid.)

Statistical Analysis

Basic descriptive analyses were conducted to ascertain frequencies of all HPV types detected and associations with sociodemographic data, health-related behaviors, and sexual history characteristics. Bivariate and multivariable logistic regression analyses were then conducted to identify risk factors for infection with HPV types associated with OPSCC (HPV-16 and HPV-18) and with Heck disease (HPV-13 and HPV-32). All data were stratified by sex. Differences were denoted to be statistically significant when 95% CIs did not overlap, and the χ^2 *P* value in 2-tailed tests was less than .05. Odds ratios (ORs) with 95% CIs were calculated in the multivariable analyses. SAS version 9.4 (SAS Institute) was used for all analyses.

Results

A total of 910 β-globin–positive saliva samples were collected from Indigenous residents of South Australia aged 18 years or older. Among participants, the median (interquartile range [IQR]) age was 37 (27-51) years, with a median (IQR) age of 37 (27-49) years for men and 38 (27-52) years for women. More than half (51.6%; 95% CI, 48.4%-54.9%) of participants were aged 37 years or older (**Table 1**). Two-thirds (65.4%; 95% CI, 62.3%-68.5%) were women and 63% resided in nonmetropolitan locations (63.0%; 95% CI, 59.8%-66.1%). Overall, 68.0% (95% CI, 65.0%-71.1%) of participants reported a highest level of eductional attainment as high school or less, and more than three-quarters (76.0%; 95% CI, 73.2%-78.8%) received their income through Centrelink. More than one-third (36.7%; 95% CI, 33.5%-40.0%) of participants had 4 or more people in their house the previous night. Fifty-five percent (55.2%; 95% CI, 52.0%-58.5%) of participants owned their own car. Nearly 60% (58.2%; 95% CI, 54.9%-61.5%) currently smoked tobacco, and approximately 12% (11.6%; 95% CI, 9.5%-13.8%) reported currently smoking nonprescription tobacco substitutes. Nearly one-quarter (24.1%; 95% CI, 21.2%-26.9%) of participants consumed alcohol on a weekly basis, while approximately 21.1% (95% CI, 18.4%-23.7%) reported currently using recreational drugs. Two percent (2.0%; 95% CI, 1.1%-2.9%) of participants reported having ever had an HPV infection, but 17.1% (95% CI, 14.6%-19.6%) did not know. Approximately 8% (8.3%; 95% CI, 6.5%-10.1%) had been vaccinated against HPV (bearing in mind most participants would not have been eligible for free public HPV vaccination), although 34.1% (95% CI, 31.0%-37.2%) did not know their vaccination status. Approximately 13% (12.9%; 95% CI, 10.7%-15.1%) reported having had a tonsillectomy. Nearly two-thirds (65.4%; 95% CI, 62.1%-68.6%) of participants reported having passionately kissed 4 or more people, 64.6% (95% CI, 61.3%-67.9%) had given oral sex, and 64.7% (95% CI, 61.4%-68.0%) had received oral sex. Almost all (94.8%; 95% CI, 93.2%-96.3%) participants reported having had sexual intercourse, with 40% commencing sexual activity before the age of 16 years, with 64.0% of participants (95% CI, 60.5%-67.4%) reporting 4 or more sexual partners over their lifetime. Nearly all (93.6%; 95% CI, 92.0%-95.3%) participants reported sexual encounters with people

Table 1. Sociodemographic Characteristics, Health-Related Behaviors, and Sexual History, Stratified by Sex

Characteristic	HPV-OPC study, % (95% CI)		
	All (N = 910)	Men (n = 315)	Women (n = 595)
Total	100	34.6 (31.5-37.7)	65.4 (62.3-68.5)
Age, y			
≥37	51.6 (48.4-54.9)	51.7 (46.2-57.3)	51.6 (47.6-55.6)
<37	48.4 (45.1-51.6)	48.3 (42.7-53.8)	48.4 (44.4-52.4)
Geographic location			
Nonmetropolitan	63.0 (59.8-66.1)	60.8 (55.4-66.3)	64.1 (60.3-68.0)
Metropolitan	37.0 (33.9-40.2)	39.2 (33.7-44.6)	35.9 (32.0-39.8)
Level of education			
High school	68.0 (65.0-71.1)	60.8 (55.4-66.3)	66.7 (62.8-70.5)
Trade/TAFE/university[a]	32.0 (28.9-35.0)	39.2 (33.7-44.6)	33.3 (29.5-37.2)
Income[b]			
Centrelink or other	76.0 (73.2-78.8)	69.2 (64.1-74.4)	79.6 (76.3-82.8)
Job	24.0 (21.2-26.8)	30.8 (25.6-35.9)[d]	20.4 (17.2-23.8)
Health care card ownership[c]			
Yes	78.8 (76.1-81.5)	76.7 (71.8-81.5)	79.9 (76.6-83.2)
No	21.2 (18.5-23.9)	23.3 (18.5-28.2)	20.1 (16.8-23.4)
People in house previous night, No.			
≥4	36.7 (33.5-40.0)	34.5 (28.9-40.1)	37.9 (33.8-42.0)
<4	63.3 (60.0-66.5)	65.5 (59.9-71.1)	62.1 (58.0-66.2)
Own car			
No	44.8 (41.5-48.0)	45.2 (39.6-50.7)	44.6 (40.6-48.6)
Yes	55.2 (52.0-58.5)	54.8 (49.3-60.4)	55.4 (51.4-59.4)
Tobacco smoking status			
Current	58.2 (54.9-61.5)	65.9 (60.5-71.3)[d]	54.0 (49.9-58.2)
Former	12.4 (10.2-14.6)	9.6 (6.3-12.9)	14.0 (11.0-16.8)
Never	29.4 (26.3-32.4)	24.5 (19.6-29.4)	32.0 (28.1-35.9)
Alcohol consumption			
Daily	3.6 (2.4-4.8)	5.2 (2.7-7.7)	2.8 (1.4-4.1)
Weekly	24.1 (21.2-26.9)	35.9 (30.5-41.4)[d]	17.8 (14.7-20.9)
Monthly	37.1 (33.9-40.3)	32.7 (27.4-38.0)	39.4 (35.4-43.4)
Never	35.3 (32.1-38.4)	26.1 (21.2-31.1)[d]	40.1 (36.1-44.1)
Use of nonprescription tobacco substitutes, eg, vaporizer or e-cigarette			
Current	11.6 (9.5-13.8)	13.4 (9.5-17.3)	10.7 (8.1-13.2)
Former	19.1 (16.4-21.7)	22.8 (18.0-27.6)	17.1 (14.0-20.2)
Never	69.3 (66.2-72.4)	63.8 (58.3-69.2)	72.2 (68.5-76.0)
Use of recreational drugs			
Current	21.1 (18.4-23.7)	27.8 (22.9-32.9)[d]	17.4 (14.4-20.5)
Former	33.7 (30.6-36.8)	41.3 (35.9-46.8)	29.6 (25.9-33.3)
Never	45.3 (42.0-48.5)	30.8 (25.6-35.9)	53.0 (48.9-57.0)
Ever diagnosed with HPV			
Yes	2.0 (1.1-2.9)	0.3 (0.0-1.0)[d]	2.9 (1.5-4.2)
No	80.9 (78.3-83.5)	81.7 (77.3-86.0)	80.5 (77.3-83.7)
Don't know	17.1 (14.6-19.6)	18.0 (13.7-22.3)	16.6 (13.6-19.6)
Ever received HPV vaccination			
Yes	8.3 (6.5-10.1)	2.2 (0.6-3.9)[d]	11.5 (8.9-14.1)
No	57.5 (54.3-60.8)	63.1 (57.8-68.5)	54.6 (50.5-58.6)
Don't know	34.1 (31.0-37.2)	34.6 (29.3-39.9)	33.9 (30.1-37.7)
Tonsils removed			
Yes	12.9 (10.7-15.1)	9.9 (6.5-13.3)	14.5 (11.6-17.4)
No	81.9 (79.3-84.4)	80.9 (76.4-85.3)	82.4 (79.3-85.5)
Don't know	5.2 (3.7-6.8)	9.2 (6.5-13.3)	3.1 (1.7-4.5)

(continued)

Table 1. Sociodemographic Characteristics, Health-Related Behaviors, and Sexual History, Stratified by Sex (continued)

Characteristic	HPV-OPC study, % (95% CI)		
	All (N = 910)	Men (n = 315)	Women (n = 595)
In life, how many passionately kissed			
≥4	65.4 (62.1-68.6)	69.5 (64.1-75.0)	63.2 (29.1-67.3)
<4	34.6 (31.4-37.9)	30.5 (25.0-35.9)	36.8 (32.7-40.9)
Ever given oral sex			
Yes	64.6 (61.3-67.9)	63.0 (57.3-68.7)	65.4 (61.4-69.5)
No	35.4 (32.1-38.7)	37.0 (31.3-42.7)	34.6 (30.5-38.6)
If yes, age when first gave oral sex, y			
<16	24.6 (20.8-28.3)	28.6 (21.8-35.3)	22.5 (18.1-27.0)
≥16	75.4 (71.7-79.2)	71.4 (64.7-78.2)	77.5 (73.0-81.9)
People given oral sex to in lifetime, No.			
>3	44.3 (40.0-48.6)	54.6 (47.1-62.1)[d]	39.1 (34.0-44.3)
≤3	55.7 (51.4-60.0)	45.4 (37.9-52.9)	60.9 (55.7-66.0)
Ever received oral sex			
Yes	64.7 (61.4-68.0)	68.0 (62.5-73.5)	62.9 (58.8-67.1)
No	35.3 (32.0-38.6)	32.0 (26.5-37.5)	37.1 (32.9-41.2)
If yes, age when first received oral sex, y			
<16	28.4 (24.5-32.3)	42.0 (34.9-49.1)[d]	20.4 (16.0-24.9)
≥16	71.6 (67.7-75.5)	58.0 (50.9-65.1)	79.6 (75.1-84.0)
People received oral sex from in lifetime, No.			
>3	49.9 (45.6-54.2)	68.6 (61.9-75.3)[d]	39.1 (33.7-44.4)
≤3	50.1 (45.8-54.4)	31.4 (24.7-38.1)	60.9 (55.6-66.3)
Sexual intercourse with another person			
Yes	94.8 (93.2-96.3)	95.3 (92.7-97.8)	94.5 (92.6-96.5)
No	5.2 (3.7-6.8)	4.7 (2.2-7.3)	5.5 (3.5-7.4)
If yes, age when first had sex, y			
<16	40.0 (36.5-43.5)	47.3 (41.2-53.4)[d]	36.2 (31.9-40.4)
≥16	60.0 (56.5-63.5)	52.7 (46.6-58.8)	63.8 (59.6-68.1)
Sexual partners, No.			
≥4	64.0 (60.5-67.4)	75.1 (69.8-80.4)[d]	58.1 (53.8-62.5)
<4	36.0 (32.6-39.5)	24.9 (19.6-30.2)	41.9 (37.5-46.2)
In lifetime, sexual encounters have been mostly			
Heterosexual	93.6 (92.0-95.3)	95.6 (93.2-98.1)	92.6 (90.4-94.9)
Homosexual	0.7 (0.2-1.3)	1.5 (0.0-2.9)	0.4 (0.0-0.9)
Bisexual	5.6 (4.0-7.2)	2.9 (0.9-4.9)[d]	7.0 (4.8-9.2)
Current relationship status			
Stable long-term	50.9 (47.4-54.3)	49.6 (43.7-55.6)	51.5 (47.2-55.7)
Short-term	5.8 (4.2-7.4)	4.0 (1.7-6.3)	6.7 (4.6-8.8)
Single	43.3 (39.9-46.8)	46.4 (40.5-52.3)	41.8 (37.6-46.0)

Abbreviations: HPV, human papillomavirus; HPV-OPC, human papillomavirus-associated oropharynx cancer; TAFE, technical and further education.

[a] TAFE provides training for vocational occupations.

[b] Centrelink is the government agency responsible for welfare payments to those means-tested to be eligible.

[c] Ownership of a government-administered health care card is means-tested and enables access to services such as publicly funded dental care.

[d] Difference statistically significant as denoted by nonoverlapping 95% CIs; $P < .05$.

predominantly of the opposite sex. More than half (50.9%; 95% CI, 47.4%-54.3%) were in current, stable long-term relationships.

More than one-third (35.3%) were positive for an oral HPV infection (**Table 2**); 33.7% of men and 36.1% of women. By far the most prevalent HPV types were those associated with Heck disease (HPV-13 and HPV-32) (22.8%; 19.1% in men and 24.7% in women). The next most prevalent HPV types were those associated with OPSCC (HPV-16 and HPV-18) (3.3%; 2.9% in men and 3.5% in women). A total of 38 HPV types were found, with the number of participants per type ranging from 1 to 119. There were no participants with multiple oral HPV types.

In bivariate analysis, we found an association between having any oral HPV type (**Table 3**) and receiving income through Centrelink compared with a job (prevalence, 37.5% [95% CI, 34.8%-41.1%] vs 28.7% [95% CI, 22.7%-34.7%]). In bivariate analysis, we found an association between having an

HPV type associated with Heck disease and residing in a nonmetropolitan location compared with a metropolitan location (prevalence, 28.5% [95% CI, 24.8%-32.3%] vs 13.1% [9.5%-16.7%]), not owning a car compared with owning a car (prevalence, 28.0% [95% CI, 23.6%-32.4%] vs 18.5% [95% CI, 15.1%-21.9%]), having not had a tonsillectomy compared with having had a tonsillectomy (prevalence, 24.1% [95% CI, 20.9%-27.2%] vs 14.0% [95% CI, 7.6%-20.4%]), having never given oral sex compared with having given oral sex (prevalence, 27% [95% CI, 22.3%-32.6%] vs 18.7% [95%

Table 2. Oral HPV Types Among 910 Indigenous Adults in South Australia

Characteristic	Participants, No. (%)		
	Total	Men	Women
Total	910 (100.0)	315 (100.0)	595 (100.0)
Positive ≥1 oral HPV type	321 (35.3)	106 (33.7)	215 (36.1)
Positive oral			
HPV-13 and/or HPV-32	207 (22.8)	60 (19.1)	147 (24.7)
HPV-16 and/or HPV-18	30 (3.3)	9 (2.9)	21 (3.5)
HPV type			
3	2 (0.2)	0	2 (0.3)
6	3 (0.3)	2 (0.6)	1 (0.2)
7	1 (0.1)	1 (0.3)	0
10	1 (0.1)	0	1 (0.2)
13	88 (9.7)	27 (8.6)	61 (10.3)
16	14 (1.5)	4 (1.3)	10 (1.7)
18	16 (1.8)	5 (1.6)	11 (1.9)
30	2 (0.2)	2 (0.6)	0
31	1 (0.1)	1 (0.3)	0
32	119 (13.1)	33 (10.5)	86 (14.5)
33	1 (0.1)	0	1 (0.2)
34	1 (0.1)	1 (0.3)	0
35	3 (0.3)	2 (0.6)	1 (0.2)
39	2 (0.2)	2 (0.6)	0
40	1 (0.1)	1 (0.3)	0
42	1 (0.1)	1 (0.3)	0
44	1 (0.1)	1 (0.3)	0
45	3 (0.3)	3 (1.0)	0
51	1 (0.1)	0	1 (0.2)
52	2 (0.2)	0	2 (0.3)
53	2 (0.2)	1 (0.3)	1 (0.2)
54	1 (0.1)	0	1 (0.2)
56	4 (0.4)	2 (0.6)	2 (0.3)
58	5 (0.6)	3 (1.0)	2 (0.3)
59	5 (0.6)	3 (1.0)	2 (0.3)
62	1 (0.1)	0	1 (0.2)
66	9 (1.0)	3 (1.0)	6 (1.0)
67	2 (0.2)	1 (0.3)	1 (0.2)
68	1 (0.1)	0	1 (0.2)
69	8 (0.9)	3 (1.0)	5 (0.8)
72	7 (0.8)	1 (0.3)	6 (1.0)
73	1 (0.1)	0	1 (0.2)
81	3 (0.3)	1 (0.3)	2 (0.3)
82	1 (0.1)	0	1 (0.2)
84	1 (0.1)	0	1 (0.2)
87	1 (0.1)	1 (0.3)	0
90	5 (0.6)	1 (0.3)	4 (0.7)
106	1 (0.1)	0	1 (0.2)

Abbreviation: HPV, human papillomavirus.

Table 3. Bivariate and Multivariable Associations With Prevalence of All Oral HPV Types, Stratified by Sex

Characteristic	All (N = 910)		Men (n = 315)		Women (n = 595)	
	Prevalence, % (95% CI)	OR (95% CI)	Prevalence, % (95% CI)	OR (95% CI)	Prevalence, % (95% CI)	OR (95% CI)
Overall HPV infection	35.3 (32.2-38.4)	NA	33.7 (28.4-38.9)	NA	36.1 (32.3-40.0)	NA
Age group, y						
<37	34.1 (29.7-38.5)	1 [Reference]	33.6 (26.0-41.0)	1 [Reference]	34.4 (28.9-39.9)	1 [Reference]
≥37	36.4 (32.0-40.7)	0.97 (0.58-1.64)	33.7 (26.4-41.0)	0.77 (0.24-2.48)	37.8 (32.3-43.2)	1.09 (0.58-2.05)
Geographic location						
Nonmetropolitan	37.1 (33.1-41.0)	0.81 (0.50-1.31)	36.1 (29.3-43.0)	0.74 (0.25-2.21)	37.5 (32.7-42.4)	0.79 (0.44-1.43)
Metropolitan	32.4 (27.4-37.5)	1 [Reference]	30.1 (21.9-38.2)	1 [Reference]	33.8 (27.4-40.2)	1 [Reference]
Level of education						
Trade/TAFE/university	33.4 (28.0-38.9)	1 [Reference]	28.3 (19.0-37.5)	1 [Reference]	35.9 (29.1-42.7)	1 [Reference]
≤High school	36.3 (32.5-40.2)	0.86 (0.52-1.41)	35.7 (29.4-42.1)	1.15 (0.37-3.59)	36.7 (31.9-41.5)	0.83 (0.44-1.57)
Income						
Job	28.7 (22.7-34.7)	1 [Reference]	28.1 (19.1-37.2)	1 [Reference]	29.2 (21.0-37.3)	1 [Reference]
Centrelink or other	37.5 (34.8-41.1)[a]	1.22 (0.60-2.46)	36.5 (30.1-43.0)	1.23 (0.27-5.65)	37.9 (33.5-42.3)	0.87 (0.34-2.21)
Health care card ownership						
No	32.1 (25.3-38.8)	1 [Reference]	33.3 (22.1-44.5)	1 [Reference]	31.3 (22.8-39.8)	1 [Reference]
Yes	37.0 (33.4-40.6)	1.09 (0.53-2.25)	35.2 (29.0-41.5)	1.19 (0.25-5.71)	37.9 (33.4-42.3)	1.25 (0.48-3.27)
People in house previous night, No.						
≤4	35.4 (31.3-39.5)	1 [Reference]	33.7 (26.8-40.6)	1 [Reference]	36.4 (31.2-41.5)	1 [Reference]
>4	33.4 (28.1-38.7)	0.76 (0.46-1.26)	32.0 (22.6-41.3)	0.44 (0.13-1.53)	34.1 (27.7-40.6)	0.91 (0.49-1.68)
Own car						
No	39.4 (34.6-44.1)	1.28 (0.74-2.23)	36.9 (28.9-44.9)	0.84 (0.21-3.31)	40.7 (34.7-46.6)	1.51 (0.76-2.99)
Yes	32.1 (28.0-36.2)	1 [Reference]	31.0 (24.0-38.0)	1 [Reference]	32.7 (27.6-37.8)	1 [Reference]
Tobacco smoking status						
Never	36.0 (30.0-41.9)	1 [Reference]	33.9 (22.9-44.6)	1 [Reference]	36.9 (29.8-44.0)	1 [Reference]
Current	34.7 (30.6-38.9)	0.64 (0.34-1.22)	33.2 (26.6-39.7)	0.17 (0.04-0.81)	35.8 (30.3-41.2)	1.02 (0.46-2.24)
Former	36.4 (27.3-45.6)	0.99 (0.47-2.10)	37.9 (20.2-55.7)	1.04 (0.20-5.33)	35.9 (25.2-46.6)	1.11 (0.43-2.88)
Alcohol consumption						
Never	36.5 (31.2-41.9)	1 [Reference]	37.5 (26.8-48.2)	1 [Reference]	36.2 (30.0-42.4)	1 [Reference]
Daily	37.5 (20.7-54.3)	0.16 (0.02-1.30)	18.8 (0.0-38.0)	0.18 (0.01-2.76)	56.3 (31.9-80.6)	NS
Weekly	34.3 (27.9-40.7)	0.95 (0.49-1.81)	31.8 (23.1-40.6)	1.18 (0.24-5.74)	36.9 (27.5-46.2)	1.03 (0.46-2.31)
Monthly	34.1 (29.0-39.3)	1.17 (0.66-2.06)	34.0 (24.7-43.3)	0.73 (0.17-3.13)	34.2 (28.0-40.4)	1.54 (0.78 (3.07)
Use of nonprescription tobacco substitutes, eg, vaporizer or e-cigarette						
Never	34.4 (30.6-38.2)	1 [Reference]	32.1 (25.4-38.8)	1 [Reference]	35.5 (30.8-40.1)	1 [Reference]
Current	43.0 (33.3-52.7)	1.35 (0.63-2.92)	37.5 (22.4-52.6)	1.91 (0.31-11.8)	46.7 (34.0-59.3)	0.94 (0.35-2.52)
Former	32.9 (25.7-40.1)	0.90 (0.51-1.58)	35.3 (23.9-46.7)	0.95 (0.27-3.29)	31.3 (21.9-40.6)	0.78 (0.37-1.62)
Use of recreational drugs						
Never	33.7 (29.1-38.4)	1 [Reference]	31.3 (21.9-40.6)	1 [Reference]	34.5 (29.2-39.8)	1 [Reference]
Current	41.8 (34.8-48.8)	1.13 (0.56-2.26)	40.2 (29.9-50.6)	2.16 (0.40-11.6)	43.1 (33.5-52.8)	1.17 (0.50-2.76)
Former	33.1 (27.8-38.4)	1.02 (0.56-1.84)	31 0 (23.0-39.0)	1.35 (0.33-5.59)	34.7 (27.6-41.8)	1.05 (0.50-2.21)
Ever diagnosed with HPV						
No	34.2 (30.7-37.6)	1 [Reference]	31.1 (25.4-36.8)	1 [Reference]	35.8 (31.5-40.1)	1 [Reference]
Yes	22.2 (3.0-41.5)	0.72 (0.21-2.52)	100	NS	17.6 (0.0-35.8)	0.46 (0.11-1.92)
Don't know	41.6 (33.8-49.4)	0.63 (0.32-1.22)	42.9 (29.8-55.9)	0.33 (0.06-1.78)	40.8 (31.1-50.6)	0.58 (0.26-1.30)
Ever received HPV vaccination						
Yes	28.0 (17.8-38.2)	1 [Reference]	42.9 (6.0-79.7)	1 [Reference]	26.5 (16.0-37.0)	1 [Reference]
No	36.6 (32.5-40.8)	1.55 (0.65-3.70)	33.5 (26.9-40.1)	0.78 (0.01-52.4)	38.5 (33.2-43.8)	1.68 (0.64-4.39)
Don't know	34.4 (29.1-39.7)	1.87 (0.78-4.47)	32.4 (23.5-41.3)	1.21 (0.02-86.7)	35.5 (28.8-42.2)	2.23 (0.86-5.77)
Tonsils removed						
Yes	33.3 (24.7-42.0)	1 [Reference]	36.7 (19.3-54.0)	1 [Reference]	32.1 (22.1-42.2)	1 [Reference]
No	35.0 (31.5-38.5)	0.79 (0.43-1.46)	33.1 (27.1-39.0)	0.48 (0.12-1.88)	36.0 (31.7-40.3)	0.85 (0.39-1.86)
Don't know	41.3 (27.0-55.6)	0.86 (0.20-3.60)	35.7 (17.9-53.6)	0.64 (0.06-7.56)	50.0 (26.8-73.2)	0.78 (0.09-7.24)

(continued)

Table 3. Bivariate and Multivariable Associations With Prevalence of All Oral HPV Types, Stratified by Sex (continued)

Characteristic	All (N = 910)		Men (n = 315)		Women (n = 595)	
	Prevalence, % (95% CI)	OR (95% CI)	Prevalence, % (95% CI)	OR (95% CI)	Prevalence, % (95% CI)	OR (95% CI)
In life, how many passionately kissed						
<4	37.5 (31.8-43.1)	1 [Reference]	38.8 (28.4-49.2)	1 [Reference]	36.9 (30.1-43.6)	1 [Reference]
≥4	33.1 (29.1-37.1)	1.07 (0.50-2.27)	30.4 (23.9-36.9)	1.54 (0.25-9.65)	34.7 (29.6-39.8)	0.87 (0.34-2.20)
Ever given oral sex						
Yes	33.3 (29.3-37.4)	NS	29.4 (22.6-36.1)	NS	35.3 (30.3-40.4)	NS
No	35.8 (30.2-41.3)	NS	37.5 (28.1-46.9)	NS	34.8 (27.9-41.7)	NS
If yes, age when first gave oral sex, y						
≥16	31.5 (26.9-36.2)	1 [Reference]	26.4 (18.6-34.2)	1 [Reference]	34.0 (28.2-39.7)	1 [Reference]
<16	38.6 (30.1-47.1)	1.36 (0.50-2.27)	36.0 (22.6-49.4)	0.72 (0.18-2.81)	40.3 (29.3-51.3)	2.35 (0.77-7.22)
People given oral sex to in lifetime, No.						
≤3	31.5 (26.1-36.9)	1 [Reference]	27.8 (17.9-37.8)	1 [Reference]	32.9 (26.5-39.2)	1 [Reference]
>3	35.7 (29.4-41.9)	1.56 (0.76-3.17)	30.5 (21.2-39.9)	1.38 (0.36-5.28)	39.3 (31.0-47.5)	1.09 (0.35-3.34)
Ever received oral sex						
Yes	32.8 (28.8-36.9)	NS	27.5 (21.1-33.9)	NS	35.9 (30.7-41.1)	NS
No	37.1 (31.5-42.7)	NS	42.7 (32.3-53.0)	NS	34.5 (27.8-41.2)	NS
If yes, age when first received oral sex, y						
≥16	31.7 (26.9-36.5)	1 [Reference]	22.0 (14.2-29.9)	1 [Reference]	35.8 (29.9-41.7)	1 [Reference]
<16	34.5 (26.7-42.2)	0.89 (0.42-1.90)	35.4 (24.8-46.1)	1.22 (0.28-5.26)	33.3 (21.9-44.8)	0.52 (0.17-1.59)
People received oral sex from in lifetime, No.						
≤3	30.4 (24.7-36.0)	1 [Reference]	20.3 (10.0-30.7)	1 [Reference]	33.3 (26.7-39.9)	1 [Reference]
>3	34.8 (28.9-40.6)	1.29 (0.62-2.69)	31.0 (23.0-39.1)	1.22 (0.21-7.25)	38.5 (30.1-47.1)	2.37 (0.75-7.49)
Sexual intercourse with another person						
Yes	34.6 (31.2-38.0)	NS	32.2 (26.5-37.9)	NS	35.9 (31.6-40.1)	NS
No	31.0 (16.9-45.0)	NS	30.7 (5.5-56.0)	NS	31.0 (14.1-47.9)	NS
If yes, age when first had sex, y						
≥16	34.1 (29.8-38.5)	NS	27.7 (20.2-35.3)	NS	36.9 (31.6-42.3)	NS
<16	36.2 (30.8-38.5)	1.14 (0.61-2.12)	37.4 (28.7-46.0)	3.68 (0.90-15.0)	35.4 (28.3-42.4)	0.83 (0.38-1.78)
Sexual partners						
≥4	33.2 (29.0-37.4)	0.66 (0.31-1.38)	31.1 (24.5-37.7)	0.55 (0.06-4.88)	34.6 (29.1-40.1)	0.69 (0.29-1.68)
<4	37.0 (31.3-42.8)	NS	35.9 (24.1-47.8)	NS	37.4 (30.7-44.0)	NS
In lifetime, sexual encounters have been mainly						
Heterosexual	35.0 (31.6-38.4)	1 [Reference]	32.2 (26.5-37.9)	1 [Reference]	36.5 (32.2-40.7)	1 [Reference]
Homosexual	50.0 (9.9-90.1)	0.62 (0.03-12.2)	25.0 (0.0-67.7)	0.59 (0.02-21.9)	100	NA
Bisexual	26.7 (13.7-39.6)	0.44 (0.18-1.06)	37.5 (3.7-71.3)	0.46 (0.03-7.77)	24.3 (10.5-38.2)	0.37 (0.13-1.00)
Current relationship status						
Stable long-term	35.4 (30.7-40.0)	1 [Reference]	32.1 (24.2-40.0)	1 [Reference]	37.0 (31.2-42.7)	1 [Reference]
Short-term	31.9 (29.1-39.1)	1.16 (0.44-0.18)	36.4 (7.7-65.0)	4.04 (0.47-34.7)	30.6 (15.5-45.7)	0.84 (0.26-2.74)
Single	34.1 (29.1-39.1)	0.96 (0.58-1.59)	32.8 (24.6-41.0)	1.26 (0.41-3.92)	34.8 (28.6-41.1)	1.00 (0.53-1.88)

Abbreviations: HPV, human papillomavirus; NA, not applicable; NS, not significant (odds ratio for this variable is either less than 0.000 or more than 999.99); OR, odds ratio.

*Results were significant using a χ^2 test at the level of $P < .05$.

CI, 15.3%-22.0%]), having never received oral sex compared with having received oral sex (prevalence, 28.6% [95% CI, 23.3%-33.9%] vs 18.0% [95% CI, 14.6%-21.3%]), and having fewer than 4 sexual partners over a lifetime compared with having 4 or more sexual partners (prevalence, 28.1% [95% CI, 22.8%-33.5%] vs 18.4% [95% CI, 14.9%-21.8%]) (**Table 4**). In bivariate analysis, residing in a metropolitan location was associated with HPV types 16 and 18 compared with residing in a nonmetropolitan location (prevalence, 5.7% [95% CI, 3.1%-8.1%] vs 1.9% [95% CI, 0.8%-3.1%]) (**Table 5**). In multivariable analyses, the odds of oral HPV-13 or HPV-32 infection was over 2 times higher among those residing in a nonmetropolitan location compared with participants with metropolitan residence (OR, 2.06 [95% CI, 1.10-3.88]) and for participants who had not had a

Table 4. Bivariate and Multivariable Associations With Prevalence of Oral HPV Types 13 and 32, Stratified by Sex

Characteristic	All (N = 910)		Men (n = 315)		Women (n = 595)	
	Prevalence, % (95% CI)	OR (95% CI)	Prevalence, % (95% CI)	OR (95% CI)	Prevalence, % (95% CI)	OR (95% CI)
Overall HPV-13 or HPV-32 infection	22.7 (20.0-25.5)	NA	19.0 (14.7-23.4)	NA	24.7 (21.2-28.2)	NA
Age, y						
<37	22.7 (18.8-26.7)	1 [Reference]	21.7 (15.1-28.3)	1 [Reference]	23.3 (18.4-28.2)	1 [Reference]
≥37	22.8 (19.0-26.6)	0.71 (0.36-1.40)	16.6 (10.8-22.3)	0.71 (0.21-2.34)	26.1 (21.1-31.0)	0.89 (0.42-1.90)
Geographic location						
Metropolitan	13.1 (9.5-16.7)	1 [Reference]	9.8 (4.5-15.0)	1 [Reference]	15.0 (10.2-19.8)	1 [Reference]
Nonmetropolitan	28.5 (24.8-32.2)[a]	2.06 (1.10-3.88)[a]	25.1 (18.9-31.3)[a]	2.80 (0.80-9.79)	30.2 (25.6-34.8)[a]	1.82 (0.88-3.76)
Level of education						
Trade/TAFE/university	18.8 (14.3-23.30	1 [Reference]	12.0 (5.3-18.6)	1 [Reference]	22.1 (16.2-27.9)	1 [Reference]
≤High school	24.7 (21.3-28.1)	1.08 (0.57-2.07)	22.2 (16.7-27.7)	1.31 (0.36-4.78)	26.2 (21.8-30.5)	1.05 (0.50-2.24)
Income						
Job	19.0 (13.7-24.2)	1 [Reference]	16.7 (9.2-24.2)	1 [Reference]	20.8 (13.5-28.1)	1 [Reference]
Centrelink or other	23.9 (20.7-27.1)	1.21 (0.49-2.99)	20.4 (15.0-25.8)	0.62 (0.14-2.79)	25.5 (21.5-29.4)	0.98 (0.33-2.88)
Health care card ownership						
No	21.7 (15.8-27.7)	1 [Reference]	20.3 (10.7-29.8)	1 [Reference]	22.6 (14.9-30.3)	1 [Reference]
Yes	20.9 (20.1-26.4)	0.75 (0.30-1.88)	18.9 (13.8-24.1)	0.70 (0.14-3.58)	25.3 (21.4-29.4)	0.89 (0.2-2.75)
People in house previous night, No.						
<4	21.5 (18.0-25.0)	1 [Reference]	17.4 (11.9-22.9)	1 [Reference]	23.8 (19.2-28.3)	1 [Reference]
≥4	24.9 (20.1-29.8)	0.94 (0.50-1.76)	21.6 (13.4-29.9)	0.82 (0.24-2.88)	26.4 (20.4-32.5)	1.01 (0.50-2.07)
Own car						
Yes	18.5 (15.1-21.9)	1 [Reference]	14.0 (8.8-19.3)	1 [Reference]	20.8 (16.4-25.2)	1 [Reference]
No	28.0 (23.6-32.4)[a]	1.02 (0.51-2.03)	24 8 (17.7-32.0)	1.20 (0.33-4.38)	29.7 (24.1-35.2)	1.19 (0.55-2.61)
Tobacco smoking						
Never	24.1 (18.8-29.4)	1 [Reference]	18.9 (9.9-27.9)	1 [Reference]	26.3 (19.8-32.7)	1 [Reference]
Current	23.4 (19.6-27.1)	1.26 (0.57-2.82)	20.1 (14.5-25.7)	0.70 (0.15-3.21)	25.5 (20.6-30.4)	1.57 (0.61-4.06)
Former	15.0 (8.2-21.7)	0.82 (0.28-2.36)	10.3 (0.0-21.5)	0.94 (0.14-6.44)	16.7 (8.4-25.0)	0.72 (0.20-2.60)
Alcohol consumption						
Never	22.8 (18.1-27.4)	1 [Reference]	22.5 (13.3-31.7)	1 [Reference]	22.8 (17.4-28.3)	1 [Reference]
Daily	28.1 (12.5-43.7)	NS	6.3 (0.0-18.2)	NS	50.0 (25.4-74.6)	NS
Weekly	21.1 (15.6-26.6)	1.17 (0.51-2.69)	18.2 (10.9-25.4)	NS	24.3 (16.0-32.6)	1.04 (0.39-2.77)
Monthly	22.6 (18.0-27.1)	1.57 (0.77-3.21)	18.0 (10.4-25.6)	NS	24.6 (19.0-30.2)	1.89 (0.84-4.26)
Use of nonprescription tobacco substitutes, eg, vaporizer or electronic cigarette						
Never	23.5 (20.1-26.9)	1 [Reference]	19.5 (13.8-25.1)	NS	25.4 (21.1-29.6)	1 [Reference]
Current	27.0 (18.3-35.7)	1.03 (0.40-2.63)	17.5 (5.6-29.3)	NS	33.3 (21.4-45.3)	0.79 (0.25-2.50)
Former	17.1 (11.3-22.8)	0.46 (0.21-1.02)	19.1 (9.7-28.5)	NS	15.6 (8.3-22.9)	0.41 (0.16-1.090
Use of recreational drugs						
Never	24.9 (20.7-29.1)	1 [Reference]	20.8 (12.7-29.0)	1 [Reference]	26.1 (21.2-31.0)	1 [Reference]
Current	25.9 (19.7-32.2)	0.71 (0.30-1.66)	25.3 (16.1-34.5)	1.48 (0.29-7.58)	26.5 (17.9-35.1)	0.72 (0.26-1.99)
Former	17.2 (12.9-21.5)	0.55 (0.26-1.17)	13.2 (7.3 -19.0)	0.44 (0.09-2.26)	20.2 (14.2-26.2)	0.65 (0.27-1.57)
Ever diagnosed with HPV						
No	21.8 (18.8-24.8)	1 [Reference]	16.5 (11.9-21.1)	NS	24.6 (20.7-28.5)	1 [Reference]
Yes	11.1 (0.0-25.7)	0.56 (0.1-3.01)	0	NS	11.8 (0.0-27.1)	0.37 (0.06-2.16)
Don't know	28.6 (21.4-35.7)	0.71 (0.31-1.62)	30.4 (18.2-42.5)	NS	27.6 (18.7-36.4)	0.57 (0.21-1.53)
Ever received HPV vaccination						
Yes	17.3 (8.7-25.9)	1 [Reference]	28.6 (0.0-62.2)	NS	16.2 (7.4-25.0)	NS
No	24.3 (20.6-28.0)	1.53 (0.52-4.51)	18.8 (13.3-24.3)	NS	27.6 (22.7-32.5)	1.39 (0.45-4.29)
Don't know	21.4 (16.8-26.0)	1.69 (0.58-4.94)	18.5 (11.2-25.9)	NS	23.0 (17.2-28.8)	1.77 (0.59-5.35)
Tonsils removed						
Yes	14.0 (7.6-20.4)[a]	1 [Reference]	6.7 (0.0-15.6)	NS	16.7 (8.7-24.7)	1 [Reference]
No	24.1 (20.9-27.2)	2.74 (1.05-7.16)[a]	21.2 (16.1-26.4)	NS	25.5 (21.6-29.4)	2.09 (0.72-6.04)
Don't know	23.9 (11.6-36.3)	1.76 (0.25-12.5)	17.9 (3.6-32.1)	NS	33.3 (11.5-55.2)	0.69 (0.04-12.9)

(continued)

Table 4. Bivariate and Multivariable Associations With Prevalence of Oral HPV Types 13 and 32, Stratified by Sex (continued)

Characteristic	All (N = 910)		Men (n = 315)		Women (n = 595)	
	Prevalence, % (95% CI)	OR (95% CI)	Prevalence, % (95% CI)	OR (95% CI)	Prevalence, % (95% CI)	OR (95% CI)
In life, how many passionately kissed						
≥4	19.7 (16.3-23.0)	0.81 (0.33-1.97)	14.9 (9.9-20.0)	0.32 (0.08-1.29)	22.4 (17.9-26.8)	0.91 (0.32-2.61)
<4	26.9 (21.7-32.0)	NA	28.2 (18.6-37.9)	NA	26.3 (20.1-32.4)	NA
Ever given oral sex						
Yes	18.7 (15.3-22.0)[a]	NS	11.3 (6.6-16.0)[a]	NS	22.4 (18.0-26.8)	NS
No	27.4 (22.3-32.6)	NS	30.8 (21.8-39.7)	NS	25.5 (19.2-31.9)	NS
If yes, age when first gave oral sex, y						
≥16	17.2 (13.4-20.9)	1 [Reference]	9.6 (4.3-14.8)	NS	20.8 (15.8-25.7)	1 [Reference]
<16	23.6 (16.2-31.0)	1.64 (0.61-4.40)	16.0 (5.7-26.3)	NS	28.6 (18.4-38.7)	2.50 (0.65-9.64)
People given oral sex to in lifetime, No.						
>3	17.0 (12.1-21.8)	2.07 (0.83-5.16)	10.5 (4.3-16.8)	1.58 (0.43-5.73)	21.5 (14.5-28.4)	1.53 (0.39-6.00)
≤3	20.1 (15.4-24.7)	NA	12.7 (5.3-20.1)	NA	22.9 (17.1-28.6)	NA
Ever received oral sex						
Yes	18.0 (14.6-21.3)[a]	NS	10.1 (5.7-14.4)[a]	NS	22.5 (18.0-27.0)	NS
No	28.6 (23.3-33.9)	NS	36.0 (25.9-46.0)	NS	25.3 (19.1-31.4)	NS
If yes, age when first received oral sex, y						
≥16	18.3 (14.3-22.3)	1 [Reference]	9.2 (3.7-14.6)	NS	22.2 (17.1-27.3)	1 [Reference]
<16	15.2 (9.3-21.0)	0.52 (0.19-1.44)	11.4 (4.3-18.5)	NS	19.7 (10.1-29.3)	0.45 (0.12-1.73)
People received oral sex from in lifetime, No.						
≤3	19.8 (15.0-24.7)	1 [Reference]	8.5 (1.3-15.6)	NS	23.2 (17.3-29.1)	1 [Reference]
>3	15.2 (10.8-19.7)	0.83 (0.33-2.13)	10.9 (5.4-16.3)	NS	19.7 (12.7-26.6)	1.29 (0.32-5.21)
Sexual intercourse with another person						
Yes	22.0 (19.0-24.9)	NS	18.0 (13.3-22.7)	NS	24.0 (20.3-27.8)	NS
No	19.0 (7.1-30.9)	NS	23.1 (0.0-46.1)	NS	17.2 (3.4-31.0)	NS
If yes, age when first had sex, y						
≥16	22.2 (18.3-26.0)	1 [Reference]	16.8 (10.5-23.1)	1 [Reference]	24.5 (19.7-29.3)	1 [Reference]
<16	22.3 (17.5-27.0)	1.17 (0.54-2.52)	19.5 (12.5-26.6)	NS	24.2 (17.8-30.5)	0.90 (0.37-2.19)
Sexual partners						
<4	28.1 (22.8-33.5)	1 [Reference]	29.7 (18.4-41.0)	NS	27.7 (21.5-33.8)	1 [Reference]
≥4	18.4 (14.9-21.8)[a]	0.77 (0.31-1.94)	14.0 (9.1-18.9)	NS	21.3 (16.6-26.1)	0.79 (0.28-2.19)
In lifetime, sexual encounters have been mainly						
Heterosexual	22.3 (19.4-25.3)	1 [Reference]	18.4 (13.7-23.1)	NS	24.4 (20.6-28.3)	1 [Reference]
Homosexual	33.3 (0.0-71.1)	NS	0	NS	100	NS
Bisexual	11.1 (1.9-20.3)	0.53 (0.116-1.75)	25.0 (0.0-55.2)	NS	8.1 (0.0-16.9)	0.30 (0.07-1.22)
Current relationship status						
Stable long-term	22.3 (18.3-26.3)	1 [Reference]	19.7 (13.0-26.4)	1 [Reference]	23.6 (18.5-28.6)	1 [Reference]
Short-term	21.3 (9.6-33.0)	1.06 (0.33-3.46)	18.2 (0.0-41.1)	0.67 (0.04-11.4)	22.2 (8.6-35.8)	1.00 (0.26-3.89)
Single	21.3 (17.0-25.6)	0.90 (0.48-1.70)	17.2 (10.6-23.8)	0.80 (0.24-2.66)	23.7 (18.1-29.2)	1.02 (0.48-2.17)

Abbreviations: HPV, human papillomavirus; NA, not applicable; NS, not significant (odds ratio for this variable either less than 0.000 or greater than 999.99); OR, odds ratio.

[a] Results were significant using a χ^2 test at the level of $P < .05$.

tonsillectomy compared with those who had received the procedure (OR, 2.74; 95% CI, 1.05-7.16) (Table 4). In multivariable analysis, the risk of HPV-16 or HPV-18 infection persisted among women with trade, TAFE, or university education (4.5%; 95% CI, 2.1%-6.9%) (Table 5).

Discussion

Consistent with our hypothesis, the prevalence of any oral HPV type, HPV types associated with Heck disease (HPV-13 and HPV-32), and HPV types associated with OPSCC (HPV-16 and HPV-18) among Indigenous Australians appeared to be higher than those reported both in other Australian

Table 5. Bivariate and Multivariable Associations With Prevalence of Oral HPV Types 16 and 18, Stratified by Sex

Characteristic	All (N = 910)		Men (n = 315)		Women (n = 595)	
	Prevalence, % (95% CI)	OR (95% CI)	Prevalence, % (95% CI)	OR (95% CI)	Prevalence, % (95% CI)	OR (95% CI)
Overall HPV-16 or HPV-18 infection	3.3 (2.1-4.5)	NA	2.9 (1.0-4.7)	NA	3.5 (2.0-5.0)	NA
Age, y						
<37	3.4 (1.7-5.1)	1 [Reference]	2.6 (0.1-5.1)	1 [Reference]	2.9 (1.6-6.0)	1 [Reference]
≥37	3.2 (1.6-4.8)	0.72 (0.13-4.05)	3.1 (0.4-5.7)	2.61 (0.23-29.8)	3.3 (1.3-5.2)	0.48 (0.08-2.93)
Geographic location						
Metropolitan	5.7 (3.1-8.1)	1 [Reference]	2.4 (0.0-5.2)	1 [Reference]	7.5 (4.0-11.1)	1 [Reference]
Nonmetropolitan	1.9 (0.8-3.1)[a]	0.18 (0.02-1.34)	3.1 (0.7-5.6)	0.29 (0.03-2.89)	1.3 (0.2-2.5)[a]	0.53 (0.10-2.77)
Level of education						
Trade/TAFE/university	4.5 (2.1-6.9)	1 [Reference]	3.3 (0.0-6.9)	1 [Reference]	5.1 (2.0-8.2)	1 [Reference]
≤High school	2.8 (1.5-4.1)	0.40 (0.08-2.02)	2.7 (0.6-4.9)	0.72 (0.05-10.1)	2.8 (1.2-4.5)	0.16 (0.03-0.97)[a]
Income						
Job	2.3 (0.3-4.3)	1 [Reference]	3.1 (0.0-6.6)	1 [Reference]	1.7 (0.0-4.0)	1 [Reference]
Centrelink or other	3.7 (2.2-5.1)	1.72 (0.21-14.0)	2.8 (0.6-5.0)	0.41 (0.03-5.70)	4.1 (2.3-5.9)	6.19 (0.35-108.5)
Health care card ownership						
No	1.6 (0.0-3.5)	1 [Reference]	2.9 (0.0-6.9)	1 [Reference]	0.9 (0.0-2.6)	1 [Reference]
Yes	3.8 (2.4-5.2)	5.80 (0.41-82.4)	3.1 (0.8-5.3)	6.06 (0.19-198.8)	4.2 (2.3-6.0)	2.03 (0.10-40.7)
People in house previous night, No.						
<4	3.8 (2.2-5.5)	1 [Reference]	3.3 (0.7-5.8)	1 [Reference]	4.1 (2.0-6.2)	1 [Reference]
≥4	1.6 (0.2-3.1)	0.26 (0.03-2.50)	3.1 (0.0-6.6)	0.46 (0.03-6.96)	1.0 (0.0-2.3)	0.19 (0.02-2.00)
Car ownership						
Yes	3.8 (2.1-5.5)	1 [Reference]	4.7 (1.5-7.9)	1 [Reference]	3.4 (1.4-5.3)	1 [Reference]
No	2.7 (1.1-4.3)	0.46 (0.07-3.23)	0.7 (0.0-2.1)	NS	3.8 (1.5-6.1)	0.64 (0.09-4.58)
Tobacco smoking						
Never	4.3 (1.8-6.9)	1 [Reference]	5.4 (0.2-10.6)	1 [Reference]	3.9 (1.1-6.8)	1 [Reference]
Current	2.0 (0.8-3.2)	0.67 (0.08-5.95)	1.5 (0.0-3.2)	1.61 (0.12-21.7)	2.3 (0.6-4.0)	0.28 (0.04-2.04)
Former	6.5 (1.8-11.2)	2.05 (0.23-18.4)	3.4 (0.0-10.1)	2.27 (0.09-55.6)	7.7 (1.8-13.6)	0.80 (0.09-6.92)
Alcohol consumption						
Daily	0	NS	0	NS	0	NS
Weekly	2.8 (0.6-5.0)	NS	2.7 (0.0-5.8)	NS	2.9 (0.0-6.2)	NS
Monthly	4.6 (2.3-6.8)	NS	5.0 (0.7-9.3)	NS	4.4 (1.7-7.1)	NS
Never	2.9 (1.0-4.7)	NS	1.3 (0.0-3.7)	NS	3.4 (1.1-5.8)	NS
Use of nonprescription tobacco substitutes, eg, vaporizer or electronic cigarette						
Current	2.0 (0.0-4.7)	NS	0	NS	3.3 (0.0-7.9)	NS
Former	4.3 (1.2-7.4)	NS	5.9 (0.3-11.5)	NS	3.1 (0.0-6.6)	NS
Never	3.4 (1.9-4.8)	NS	2.6 (0.3-4.9)	NS	3.7 (1.9-5.5)	NS
Use of recreational drugs						
Current	2.1 (0.1-4.2)	NA	1.1 (0.0-3.4)	NA	2.9 (0.0-6.2)	NA
Former	4.6 (2.3-7.0)	NA	3.9 (0.5-7.2)	NA	5.2 (1.9-8.5)	NA
Never	3.0 (1.3-4.6)	NA	3.1 (0.0-6.6)	NA	2.9 (1.0-4.8)	NA
Ever diagnosed with HPV						
Yes	5.6 (0.0-16.2)	1 [Reference]	100	NS	0	NS
No	3.3 (2.0-4.6)	6.83 (0.46-101.3)	2.4 (0.5-4.2)	NS	3.8 (2.1-5.5)	NS
Don't know	3.2 (0.4-6.1)	0.59 (0.04-9.07)	3.6 (0.0-8.5)	NS	3.1 (0.0-6.5)	NS
Ever received HPV vaccination						
Don't know	3.6 (1.5-5.6)	1 [Reference]	2.8 (0.0-5.9)	NA	4.0 (1.3-6.7)	1 [Reference]
Yes	5.3 (0.2-10.4)	1.07 (0.07-17.3)	0	NS	5.9 (0.3-11.5)	0.22 (0.02-2.66)
No	2.9 (1.4-4.3)	0.89 (0.05-15.2)	3.0 (0.6-5.5)	NS	2.8 (1.0-4.6)	0.66 (0.08-5.73)
Tonsils removed						
Yes	3.5 (0.1-6.9)	1 [Reference]	0	NS	4.8 (0.2-9.3)	NS
No	2.9 (1.7-4.1)	0.32 (0.06-1.81)	2.4 (0.5-4.4)	NS	3.1 (1.6-4.7)	NS
Don't know	8.7 (0.5-16.9)	2.51 (0.08-82.5)	10.7 (0.0-22.2)	NS	5.6 (0.0-16.2)	NS

(continued)

Table 5. Bivariate and Multivariable Associations With Prevalence of Oral HPV Types 16 and 18, Stratified by Sex (continued)

Characteristic	All (N = 910)		Men (n = 315)		Women (n = 595)	
	Prevalence, % (95% CI)	OR (95% CI)	Prevalence, % (95% CI)	OR (95% CI)	Prevalence, % (95% CI)	OR (95% CI)
In life, how many passionately kissed						
<4	3.5 (1.4-5.7)	1 [Reference]	2.4 (0.0-5.6)	1 [Reference]	4.0 (1.3-6.8)	1 [Reference]
≥4	3.0 (1.5-4.4)	0.55 (0.02-13.1)	2.6 (0.3-4.8)	0.90 (0.07-12.4)	3.2 (1.3-5.1)	0.54 (0.04-6.48)
Ever given oral sex						
Yes	3.2 (1.1-5.1)	NS	2.8 (0.4-5.3)	NS	3.4 (1.5-5.3)	NS
No	3.1 (1.1-5.1)	NS	1.9 (0.0-4.6)	NS	3.8 (1.0-6.6)	NS
If yes, age when first gave oral sex, y						
≥16	3.6 (1.7-5.4)	1 [Reference]	2.4 (0.0-5.1)	1 [Reference]	4.2 (1.7-6.6)	1 [Reference]
<16	2.4 (0.0-5.0)	0.36 (0.05-2.67)	4.0 (0.0-9.5)	2.19 (0.20-24.3)	1.3 (0.0-3.8)	0.72 (0.04-12.9)
People given oral sex to in lifetime, No.						
≤3	3.1 (1.1-5.1)	1 [Reference]	2.5 (0.0-6.0)	1 [Reference]	3.3 (0.9-5.8)	1 [Reference]
>3	3.5 (1.1-5.9)	3.29 (0.42-25.8)	3.2 (0.0-6.7)	1.94 (0.12-31.4)	3.7 (0.5-6.9)	1.64 (0.26-10.31)
Ever received oral sex						
Yes	2.9 (1.4-4.3)	NS	2.6 (0.3-4.9)	NS	3.0 (1.2-4.9)	NS
No	3.9 (1.6-6.1)	NS	2.2 (0.0-5.3)	NS	4.6 (1.7-7.6)	NS
If yes, age when first received oral sex, y						
≥16	2.5 (0.9-4.1)	1 [Reference]	0.9 (0.0-2.7)	NS	3.1 (1.0-5.2)	NS
<16	4.1 (0.9-7.4)	6.59 (0.90-48.3)	5.1 (0.2-9.9)	NS	3.0 (0.0-7.2)	NS
People received oral sex from in lifetime, No.						
>3	4.3 (1.8-6.8)	NS	3.9 (0.5-7.2)	NS	4.7 (1.0-8.4)	NS
≤3	1.6 (0.0-3.1)	NS	0	NS	2.0 (0.1-4.0)	NS
Sexual intercourse with another person						
Yes	3.2 (1.9-4.4)	NS	2.7 (0.7-4.7)	NS	3.4 (1.8-5.0)	NS
No	4.8 (0.0-11.2)	NS	0	NS	6.9 (0.0-16.1)	NA
If yes, age when first had sex, y						
≥16	3.8 (2.0-5.5)	NS	3.6 (0.5-6.9)	1 [Reference]	3.8 (1.7-5.9)	1 [Reference]
<16	2.3 (0.6-4.0)	NS	1.6 (0.0-3.9)	0.30 (0.02-4.29)	2.8 (0.4-5.2)	0.52 (0.05-5.00)
Sexual partners						
<4	3.0 (0.9-5.0)	1 [Reference]	1.6 (0.0-4.6)	1 [Reference]	3.4 (0.9-5.9)	1 [Reference]
≥4	3.3 (1.7-5.0)	1.06 (0.04-30.7)	3.1 (0.6-5.6)	0.23 (0.01-5.96)	3.5 (1.4-5.6)	1.71 (0.14-20.8)
In lifetime, sexual encounters have been mainly						
Heterosexual	3.5 (2.1-4.8)	NS	2.7 (0.7-4.7)	NS	3.9 (2.2-5.6)	1 [Reference]
Homosexual	0	NS	0	NS	0	NS
Bisexual	2.2 (0.0-6.5)	NS	0	NS	2.7 (0.0-7.9)	0.63 (0.04-9.05)
Current relationship status						
Stable long-term	3.4 (1.6-5.1)	1 [Reference]	2.2 (0.0-4.7)	1 [Reference]	4.0 (1.7-6.3)	NS
Short-term	2.1 (0.0-6.3)	1.76 (0.11-28.2)	9.1 (0.0-26.2)	5.59 (0.25-126.6)	0	NS
Single	3.4 91.5-5.3)	0.89 (0.18-4.46)	2.3 (0.0-5.0)	0.18 (0.01-2.72)	4.0 (1.4-6.6)	NS

Abbreviations: HPV, human papillomavirus; NA, not applicable; NS, not significant (odds ratio for this variable is either less than 0.000 or greater than 999.9); OR, odds ratio.

* Results were significant using a χ^2 test at the level of $P < .05$.

studies and in populations from other countries. The prevalence of oral HPV in the current study was 15.3 times that reported in a study of young non-Indigenous Australians[24] and 4.7 times that reported by Antonsson et al[23] in a systematic review involving 9 studies from other countries.

The prevalence of HPV-13 or HPV-32 was 0 in the Australian study. The systematic review reported no prevalence estimates for HPV-13 or HPV-32, but it is unclear if that is because the prevalence was 0 or if these estimates were not analyzed. The prevalence of HPV types associated with OPSCC in the current study was 2.5 times that reported in the Australian study and 2.1 times that reported in the review of studies from other countries.

Our additional hypothesis that risk factors would include male sex, social disadvantage, tobacco use, and early and high levels of sexual activity proved only partially true. Indicators of social disadvantage were associated with Heck disease, but so were low rates of sexual activity. There were no apparent risk factors for HPV types associated with OPSCC aside from residing in a metropolitan location. The prevalence of HPV among those having given oral sex (64.6%) was much lower in the current study than in the second Australian Study of Health and Relationships (77.0%).[31]

The high levels of oral carriage of HPV in our study are concerning, particularly the high prevalence of HPV types associated with OPSCC. It is particularly interesting that the rates were higher among women, across both younger and older demographic characteristics. The findings speak to an urgent need to ensure high HPV vaccination coverage in Indigenous adolescents (although this does not prevent infection with HPV-13 and HPV-32), particularly given the evidence of HPV vaccine efficacy in decreasing the subsequent prevalence of oral HPV infection.[32] Further research could assess the effectiveness and cost-effectiveness of immunization of those in older age groups (ie, those aged 20 years or older who are no longer eligible for free vaccination). Efforts to extend the benefits provided by vaccination would need to take into account the lower vaccine effectiveness among those already exposed to HPV and the long latent period between a causal HPV infection and invasive disease. Both the effectiveness of vaccination against persistent oral HPV infection at older ages and its cost-effectiveness are yet to be demonstrated. Australian adolescents aged up to 19 years can receive 2 doses of the HPV vaccine free of charge as part of the National HPV Vaccination Program, and HPV vaccination is also available in Australia for women aged 20 to 45 years and men aged 20 to 26 years but is not reimbursed in the public program. Evidence has shown that the level of elective uptake in women not eligible for vaccination through the publicly funded program in Australia is low (ie, 11%).[33]

The rates of oral carriage of HPV types associated with Heck disease in our study were higher than what has been presented in the literature to date. For example, in the Australian study among university students, there were no HPV-13 or HPV-32 types identified.[24] Although factors that determine susceptibility for Heck disease are unclear, genetic susceptibility—especially concerning the human lymphocytic antigen (HLA)-DR4(DRB1*0404) allele (an allele occurring frequently in Indigenous populations of the Americas but with no documented reports among Indigenous Australians)—is thought to play a major role in vulnerability to HPV-13 and HPV-32.[29] It is reassuring that HPV types associated with Heck disease are considered low risk (ie, they are not found in cancers), with spontaneous regression of clinical lesions during a mean of 18 months.[34] It is perhaps unsurprising that associations with HPV-13 and HPV-32 in our study included low sexual activity, given that Heck disease is not associated with high sexual activity.[34] The hypothesized mode of transition is horizontal (mouth-to-mouth), commencing early in infancy via the mother.[35]

The critical issue with high-risk oral HPV infections regarding OPSCC (or any HPV-related head and neck cancer) is persistent oral HPV infection. In a large cohort study of incidence and clearance of oral HPV among men who did not have HIV or anogenital cancer, Kreimer et al[36] reported that during the first 12 months of follow-up, 4.4% of men acquired an incident oral HPV infection, with 1.7% of this 4.4% being an oncogenic HPV type and 0.6% of the 4.4% being HPV-16. Acquisition of oral oncogenic HPV was significantly associated with tobacco smoking and being single and was similar across included countries, age groups, and reported sexual behaviors. The median duration of infection was 6.9 months for any oral HPV, 6.3 months for oncogenic HPV, and 7.3 months for HPV-16. Eight of the 18 incident oral HPV-16 infections (44.4%) persisted for 6 or more months. The authors concluded that newly acquired oral oncogenic HPV infections in healthy men were rare and that most cleared within 1 year. The incidence, clearance, or persistence of oral HPV infections among Indigenous Australians remains unknown and is the subject of continuing research.

Limitations

This study has limitations. It did not include clinical dental examinations, which would have revealed any physical manifestations of both Heck disease and early-stage OPSCC. The study was not

representative, with almost two-thirds of participants being women. Oral carriage of HPV is usually higher among men, and because only 35% of participants in our study were men, our findings may underestimate the true prevalence of oral HPV in the Indigenous population. The difficulties in recruiting men to health-related studies is widely documented,[37,38] including in the Indigenous Australian context.[30] We found no association between sex and HPV infection in our sample. Conversely, given that we found that higher HPV prevalence was associated with living in nonmetropolitan areas and that people living in these areas were overrepresented in our sample compared with the Indigenous population in South Australia, this may have overestimated prevalence. In direct comparisons with other studies, this study did not age match.

Conclusions

In this study, the overall prevalence of HPV detected in oral fluid in a large convenience sample of Indigenous Australians was high, with one-third demonstrating carriage on a single occasion. The most prevalent HPV types were those associated with Heck disease (HPV-13 and HPV-32). The next most prevalent were types most strongly associated with OPSCC (HPV-16 and HPV-18). Prevalence of these types appeared to exceed both Australian and international population-level estimates.

ARTICLE INFORMATION

Accepted for Publication: February 6, 2020.

Published: June 8, 2020. doi:10.1001/jamanetworkopen.2020.4951

Corresponding Author: Lisa M. Jamieson, PhD, University of Adelaide, 57 North Terrace, Adelaide 5005, Australia (lisa.jamieson@adelaide.edu.au).

Author Affiliations: Australian Research Centre for Population Oral Health, University of Adelaide, Adelaide, Australia (Jamieson, Ju, Hedges, Sethi); QIMR Berghofer Medical Research Institute, Royal Brisbane Hospital, Brisbane, Australia (Antonsson, De Souza); Menzies School of Health Research, Spring Hill, Australia (Garvey); Cancer Council New South Wales, Sydney, Australia (Smith, Canfell); Sydney Medical School, University of Sydney, Sydney, Australia (Smith, Canfell); Adelaide Dental School, University of Adelaide, Australia (Logan); Menzies Health Institute Queensland, Griffith University and Faculty of Dentistry, Queensland, Australia (Johnson); Oral and Craniofacial Sciences, King's College, London, United Kingdom (Johnson); National Centre for Epidemiology and Population Health, ANU College of Health and Medicine, Australian National University, Australian Capital Territory, Australia (Dunbar); Strategic Partnerships, Aboriginal Health Division Women's and Children's Health Network, Adelaide, Adelaide, Australia (Leane); Aboriginal Health Council of South Australia, Adelaide, Australia (Hill); Wardliparingga Aboriginal Research Unit, South Australian Health and Medical Research Institute, Adelaide, Australia (Brown); University of South Australia School of Health Sciences, Adelaide, Australia (Roder).

Author Contributions: Dr Jamieson had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Jamieson, Garvey, Logan, Johnson, Hedges, Dunbar, Leane, Hill, Brown, Canfell.

Acquisition, analysis, or interpretation of data: Jamieson, Antonsson, Ju, Smith, Logan, Johnson, Sethi, Dunbar, Roder, De Souza, Canfell.

Drafting of the manuscript: Jamieson, Ju, Hedges, Hill.

Critical revision of the manuscript for important intellectual content: Jamieson, Antonsson, Garvey, Ju, Smith, Logan, Johnson, Sethi, Dunbar, Leane, Brown, Roder, De Souza, Canfell.

Statistical analysis: Ju, Sethi.

Obtained funding: Jamieson, Garvey, Logan, Dunbar, Leane, Canfell.

Administrative, technical, or material support: Logan, Johnson, Sethi, Hill, Brown, Roder, De Souza.

Supervision: Jamieson, Antonsson, Johnson, Canfell.

Cultural advice and support: Leane.

Conflict of Interest Disclosures: Dr Canfell reported being co-principal investigator of an investigator-initiated trial of primary human papillomavirus screening in Australia (Compass) that is conducted and funded by the Victorian Cytology Service, a government-funded health promotion charity that has received funding contributions from Roche Molecular Systems and Ventana Inc. Neither Dr Canfell nor her institution on her behalf have received funding from industry for this or any other project. Dr Garvey reported receiving salary support from the National Health and Medical Research Council (NHMRC) during the conduct of the study. Dr Smith reported receiving salary support from NHMRC and grants from Cancer Institute New South Wales during the conduct of the study. Dr Logan reported salary support from NHMRC during the conduct of the study. Dr Johnson reported salary support from NHMRC during the conduct of the study. Dr Canfell reported salary support from NHMRC Australia during the conduct of the study, and grants from Roche Molecular Systems outside the submitted work. No other disclosures were reported.

Funding/Support: This study was funded by the Australia's NHMRC under grant APP1120215.

Role of the Funder/Sponsor: The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: We thank the study participants, Indigenous Reference Group, staff who collected data, and key participating Aboriginal Community Controlled Health Organisations.

Additional Information: The original data, including all clinical and epidemiological data, used in this work will be made available upon request. Requests should be directed to the corresponding author.

REFERENCES

1. Lechner M, Breeze CE, O'Mahony JF, Masterson L. Early detection of HPV-associated oropharyngeal cancer. *Lancet*. 2019;393(10186):2123. doi:10.1016/S0140-6736(19)30227-2

2. D'Souza G, Kreimer AR, Viscidi R, et al. Case-control study of human papillomavirus and oropharyngeal cancer. *N Engl J Med*. 2007;356(19):1944-1956. doi:10.1056/NEJMoa065497

3. Hong A, Lee CS, Jones D, et al. Rising prevalence of human papillomavirus-related oropharyngeal cancer in Australia over the last 2 decades. *Head Neck*. 2016;38(5):743-750. doi:10.1002/hed.23942

4. Plummer M, de Martel C, Vignat J, Ferlay J, Bray F, Franceschi S. Global burden of cancers attributable to infections in 2012: a synthetic analysis. *Lancet Glob Health*. 2016;4(9):e609-e616. doi:10.1016/S2214-109X(16)30143-7

5. Castellsagué X, Alemany L, Quer M, et al; ICO International HPV in Head and Neck Cancer Study Group. HPV involvement in head and neck cancers: comprehensive assessment of biomarkers in 3680 patients. *J Natl Cancer Inst*. 2016;108(6):djv403. doi:10.1093/jnci/djv403

6. Yakin M, Seo B, Hussaini H, Rich A, Hunter K. Human papillomavirus and oral and oropharyngeal carcinoma: the essentials. *Aust Dent J*. 2019;64(1):11-18. doi:10.1111/adj.12652

7. National Cancer Institute. Annual report to the nation on the status of cancer. Accessed September 30, 2019. https://seer.cancer.gov/report_to_nation/

8. Office for National Statistics. Cancer registration statistics, England: first release, 2016. Accessed September 30, 2019. https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/cancerregistrationstatisticsengland/2016

9. Henke RP, Guèrin-Reverchon I, Milde-Langosch K, Koppang HS, Löning T. In situ detection of human papillomavirus types 13 and 32 in focal epithelial hyperplasia of the oral mucosa. *J Oral Pathol Med*. 1989;18(7):419-421. doi:10.1111/j.1600-0714.1989.tb01575.x

10. Jayasooriya PR, Abeyratne S, Ranasinghe AW, Tilakaratne WM. Focal epithelial hyperplasia (Heck's disease): report of two cases with PCR detection of human papillomavirus DNA. *Oral Dis*. 2004;10(4):240-243. doi:10.1111/j.1601-0825.2004.01012.x

11. Bassioukas K, Danielides V, Georgiou I, Photos E, Zagorianakou P, Skevas A. Oral focal epithelial hyperplasia. *Eur J Dermatol*. 2000;10(5):395-397.

12. Ozden B, Gunduz K, Gunhan O, Ozden FO. A case report of focal epithelial hyperplasia (Heck's disease) with PCR detection of human papillomavirus. *J Maxillofac Oral Surg*. 2011;10(4):357-360. doi:10.1007/s12663-011-0184-2

13. Archard HO, Heck JW, Stanley HR. Focal epithelial hyperplasia: an unusual oral mucosal lesion found in Indian children. *Oral Surg Oral Med Oral Pathol*. 1965;20:201-212. doi:10.1016/0030-4220(65)90192-1

14. González LV, Gaviria AM, Sanclemente G, et al. Clinical, histopathological and virological findings in patients with focal epithelial hyperplasia from Colombia. *Int J Dermatol*. 2005;44(4):274-279. doi:10.1111/j.1365-4632.2005.02321.x

15. Wu JSA, Florian MC, Rodrigues DA, Tomimori J. Skin diseases in indigenous population: retrospective epidemiological study at Xingu Indigenous Park (XIP) and review of the literature. *Int J Dermatol*. 2017;56(12):1414-1420. doi:10.1111/ijd.13716

16. Eversole LR. *Clinical Outline of Oral Pathology: Diagnosis and Treatment*. People's Medical Publishing House; 2011.

17. Australian Institute of Health and Welfare. *Australia's Health, 2018*. Australian Institute of Health and Welfare; 2018.

18. Cancer Australia. *Aboriginal and Torres Strait Islander Cancer Statistics*. Australian Government; 2018.

19. Banham D, Roder D, Keefe D, et al; CanDAD Aboriginal Community Reference Group and other CanDAD Investigators. Disparities in cancer stage at diagnosis and survival of Aboriginal and non-Aboriginal South Australians. *Cancer Epidemiol*. 2017;48:131-139. doi:10.1016/j.canep.2017.04.013

20. Australian Institute of Health and Welfare. *Cancer in Aboriginal and Torres Strait Islander people of Australia*. Australian Institute of Health and Welfare; 2018.

21. Brotherton JM, Winch KL, Chappell G, et al. HPV vaccination coverage and course completion rates for Indigenous Australian adolescents, 2015. *Med J Aust*. 2019;211(1):31-36. doi:10.5694/mja2.50221

22. Garland SM, Brotherton JM, Condon JR, et al; WHINURS study group. Human papillomavirus prevalence among Indigenous and non-Indigenous Australian women prior to a national HPV vaccination program. *BMC Med*. 2011;9:104. doi:10.1186/1741-7015-9-104

23. Wood ZC, Bain CJ, Smith DD, Whiteman DC, Antonsson A. Oral human papillomavirus infection incidence and clearance: a systematic review of the literature. *J Gen Virol*. 2017;98(4):519-526. doi:10.1099/jgv.0.000727

24. Antonsson A, Cornford M, Perry S, Davis M, Dunne MP, Whiteman DC. Prevalence and risk factors for oral HPV infection in young Australians. *PLoS One*. 2014;9(3):e91761. doi:10.1371/journal.pone.0091761

25. Jamieson L, Garvey G, Hedges J, et al. Human papillomavirus and oropharyngeal cancer among Indigenous Australians: protocol for a prevalence study of oral-related human papillomavirus and cost-effectiveness of prevention. *JMIR Res Protoc*. 2018;7(6):e10503. doi:10.2196/10503

26. Australian Institute of Health and Welfare. *Housing Circumstances of Indigenous Households: Tenure and Overcrowding*. Australian Institute of Health and Welfare; 2014.

27. de Roda Husman AM, Walboomers JMM, Hopman E, et al. HPV prevalence in cytomorphologically normal cervical scrapes of pregnant women as determined by PCR: the age-related pattern. *J Med Virol*. 1995;46(2):97-102. doi:10.1002/jmv.1890460203

28. Manos MM, Ting Y, Wright DK, Lewis AJ, Broker TR. The use of polymerase chain reaction amplification for the detection of genital human papillomaviruses. *Cancer Cell*. 1989;7:209-214.

29. Garcia-Corona C, Vega-Memije E, Mosqueda-Taylor A, et al. Association of HLA-DR4 (DRB1*0404) with human papillomavirus infection in patients with focal epithelial hyperplasia. *Arch Dermatol*. 2004;140(10):1227-1231. doi:10.1001/archderm.140.10.1227

30. National Center for Biotechnology Information. BLAST: basic local alignment search tool. Accessed April 17, 2020. https://blast.ncbi.nlm.nih.gov/Blast.cgi

31. Rissel C, Badcock PB, Smith AM, et al. Heterosexual experience and recent heterosexual encounters among Australian adults: the Second Australian Study of Health and Relationships. *Sex Health*. 2014;11(5):416-426. doi:10.1071/SH14105

32. Wierzbicka M, Berkhof JH, Dikkers FG. Prophylactic human papilloma virus vaccination in head and neck: indications and future perspectives. *Curr Opin Otolaryngol Head Neck Surg*. 2019;27(2):85-90. doi:10.1097/MOO.0000000000000525

33. Mazza D, Petrovic K, Chakraborty S. HPV vaccination of adult women: an audit of Australian general practitioners. *Aust N Z J Obstet Gynaecol*. 2012;52(6):528-533. doi:10.1111/ajo.12002

34. Bennett LK, Hinshaw M. Heck's disease: diagnosis and susceptibility. *Pediatr Dermatol*. 2009;26(1):87-89. doi:10.1111/j.1525-1470.2008.00830.x

35. Syrjänen S. Oral manifestations of human papillomavirus infections. *Eur J Oral Sci*. 2018;126(suppl 1):49-66. doi:10.1111/eos.12538

36. Kreimer AR, Pierce Campbell CM, Lin HY, et al. Incidence and clearance of oral human papillomavirus infection in men: the HIM cohort study. *Lancet*. 2013;382(9895):877-887. doi:10.1016/S0140-6736(13)60809-0

37. Rounds T, Harvey J. Enrollment challenges: recruiting men to weight loss interventions. *Am J Mens Health*. 2019;13(1):1557988319832120. doi:10.1177/1557988319832120

38. Buston K. Recruiting, retaining and engaging men in social interventions: lessons for implementation focusing on a prison-based parenting intervention for young incarcerated fathers. *Child Care Pract*. 2018;24(2):164-180. doi:10.1080/13575279.2017.1420034

39. Isaacs A, Pepper H, Pyett P, Gruis H, Waples-Crowe P, Oakley Browne M. What you do is important but how you do it is more important. *Qual Res J*. 2011;11:51-61. doi:10.3316/QRJ1101051

13.5 – APPENDIX E – HPV Vaccine Systematic Review

Title: HPV Vaccine: Uptake and understanding among global Indigenous communities – A qualitative systematic review

Author Affiliations

Brianna Poirier[1], Sneha Sethi[1], Karen Canfell[2,3], Megan Smith[2,3], Gail Garvey[4], Joanne Hedges[1], Xiangqun Ju[1], Lisa Jamieson[1]

1. Adelaide Dental School, University of Adelaide, Adelaide, Australia
2. Cancer Council of New South Wales, Sydney, Australia
3. School of Public Health, University of Sydney
4. Menzies School of Health Research, Charles Darwin University, Darwin, Australia

Abstract:

Rationale: Indigenous populations have a high prevalence of Human Papillomavirus (HPV) and a high incidence of HPV associated cancers, such as cervical and oropharyngeal cancer. There is an effective HPV vaccination program in almost all countries to prevent the incidence of cervical cancer but reports suggest that the uptake of these vaccinations by Indigenous populations is low.

Objective: The objective of this qualitative systematic review was to explore the knowledge and beliefs of global Indigenous populations regarding HPV vaccines. This review was performed to identify the barriers faced by Indigenous peoples and to provide evidence for more effective and acceptable execution of vaccination policies for Indigenous peoples.

Methods: Two investigators independently searched MEDLINE, PubMed, SCOPUS and Web of Science databases using a pre-specified search strategy to identify qualitative studies on narratives of Indigenous peoples regarding HPV vaccine awareness, knowledge and experiences across all geographic and income-level settings.

Results: After performing the literature search and quality appraisals 5 papers were included in the final review. Three core synthesised findings were identified: reasons for acceptance, reasons for hesitancy and areas for improvement. Lack of correct knowledge and mistrust in the healthcare system were important categories observed in all papers included in the review. Other categories within the conceptual model include prioritising disease prevention, health professional guidance, family support and supportive community environment.

Conclusion: Qualitative systematic reviews are an excellent means of exploring the gaps in current healthcare practices. Indigenous healthcare research should be grounded in community experiences and feedback. This review provides insight into HPV vaccination understanding

and acceptance as well as a collection of recommendations for increasing resonance of vaccination strategies with Indigenous communities.

Keywords: Indigenous women health, Human papillomavirus infections, cervical cancer, qualitative systematic review, HPV vaccine

Introduction

Humans have highly evolved immune systems, which possess extraordinary abilities to recognise, remember and fight pathogens. The technology of vaccines capitalises on this ability and induces an immune response that confers protection against infection and/or disease on subsequent exposure to a pathogen[1]. This has led to a significant decline in the spread of highly infectious diseases and has given us opportunities to eradicate diseases such as polio and smallpox.

Human Papillomavirus (HPV), with more than 200 subtypes, is one of the most commonly sexually transmitted infections and is associated with cancers of cervix, oropharynx and anal carcinoma[2,3,4]. HPV infects 80 percent[5] of people at least once in their lifetime, but due to its rapid clearance rate, many people never become aware of infection. Malignant changes can be anticipated if one of the 14 high-risk HPV types are persistent in the human body for a prolonged period of time[6,7].

The two most popular and commercially available vaccines against HPV infection are Gardasil (Quadrivalent; Merck & Co., Kenilworth, NJ, USA) and Cervix (Bivalent; GSK, Brentford, UK)[8]. Although preventive vaccines have been available in the market since 2006[9], statistics[10,11] demonstrate a sharp increase in the number of reported HPV-related oropharyngeal, anal and penile lesions cases.[9,10,11] A systematic review in 2016 demonstrated that while substantial proportions of women from high- and middle-income countries were being vaccinated, women in low income countries or regions, and who are potentially at a higher risk, had difficulties accessing vaccinations. [12,13] Studies demonstrate growing inequalities in both the distribution of vaccine and uptake[14,15,16]. More recently, steps are being taken to address circumstances of inaccessible HPV vaccination programs; wholesale efforts are being made to create awareness and make vaccinations available to many disadvantaged

communities.[14,15,16] The World Health Organisation (WHO) launched a cervical cancer elimination strategy in May 2020, with three main objectives of preventing, screening, and treating HPV associated cervical cancers. The targets for the WHO strategy include 90% vaccination rates, 70% screening rates and treatment for 90% of the invasive cancers for women in all countries by the year 2030.[13]

Low vaccination rates are related to vaccine hesitancy in addition to vaccine inaccessibility. Hesitancy has been defined as an expression of concern or doubt about the value or safety of vaccination; thus, the concerns are not limited only to those who refuse to get vaccinated but also encourage others to refuse vaccination.[17] Vaccine decisions are personal and complex, hesitation for vaccinations can be attributed to a variety of factors, such as safety concerns and incorrect knowledge (1, 2). Further exploration of hesitancy is needed to identify and better understand hesitations in order to address barriers and improve vaccine uptake. Vaccination attitudes are influenced by people at every level of the healthcare system including healthcare workers, healthcare professionals, community members and public health professionals. It has been reported that healthcare professionals have expressed difficulty in building a trustful relationship with patients leading to an information deficit[17]. Misinformation and lack of awareness has been shown as the most common reasons for developing a hesitant attitude towards vaccinations[17].

Indigenous communities bear an unfortunate burden of chronic and infectious diseases as well as poorer quality of life outcomes.[18] A high pooled prevalence of HPV in Indigenous populations has been observed[19], as compared to prevalence in general populations.[11,12] It has been suggested that health conditions of Indigenous people are over-represented among the poor and disadvantaged, especially in developed countries.[18] The Centre of Disease Control (CDC) in the United States released data which suggests that Indigenous communities carry an increased burden of infectious disease, particularly with regard to sexually transmitted

diseases.[20] While HPV vaccine coverage has been reported as high, course completion is generally lower for Indigenous adolescents.[21] Trust between Indigenous community members and healthcare workers is central to vaccination strategies, these relationships have significant implications for researchers and policy-makers. Increasing vaccination rates requires a coordinated and engaged strategy.

The objective of this qualitative systematic review was to explore the knowledge and beliefs of global Indigenous populations regarding HPV vaccines. This review was performed to identify the barriers faced by Indigenous peoples and to provide evidence for more effective and acceptable execution of vaccination policies for Indigenous peoples.

Materials and methods

This systematic review has been registered in PROSPERO (CRD42021239160) and the Joanna Briggs Systematic Reviews register. A prior search of the PROSPERO register revealed no similar studies. Both the PRISMA guidelines[1] and the Enhancing Transparency in Reporting the Synthesis of Qualitative Research (ENTREQ) statement (Table 1) were followed in the conduct of this systematic review.

Positionality

Recognising that personal experiences and opinions heavily influence research perspectives, it is critical for researchers to self-situate. This review is a result of the desire to prioritize individual voices and stories of Indigenous women and healthcare workers. After hearing first-hand accounts of various health disparities experienced by Indigenous women in South Australia, while conducting field work for a different HPV project, the primary reviewers (B.P and S.S) discussed the importance of the person behind each statistic. A desire to synthesise existing knowledge in HPV vaccine literature was established with the aim to identify future

research steps and policy actions. While both non-Indigenous researchers, B.P has qualitative experience with community-engaged scholarship in the context of Indigenous health in Canada and Australia and S.S is an oral pathologist with experience working with Indigenous populations in Australia. The supporting research team consists of Indigenous and non-Indigenous scholars with vast experience in the realm of Indigenous health research.

Identifying studies for inclusion

The reviewers used a pre-established search strategy[2]**,** which involved using terms (and their edited variants) describing the population of interest, the phenomenon being researched, as well as the included study designs (Supplementary file 1). Two investigators (B.P and S.S) independently screened the literature for eligible articles using MEDLINE, PubMed, SCOPUS and Web of Science databases from inception until 6th January 2021. For example, the search strategy used for PubMed Database was as follows: First Nation/First Nations/Pacific Islander/Pacific Islanders/Torres Strait Islander/Torres Strait* Islanders/ Aborigin*/ Alaska*/ Aleut*/ Amerind*/ American Indian/ Arctic/ Aymara/ Bushmen/ Chukchi/ Chukotka*/ Circumpolar/ Eskimo*/ Greenland*/ Hmong/ Indian*/ Indigen*/ Inuit*/ Inupiaq/ Inupiat/ Khanty/ Maori*/ Mapuche/ Metis/ Native*/ Navaho*/ Navajo*/ Nenets/ Quechua/ Saami/ Sami/ Samoan*/ Siberia*/ Skolt/ Tribal/ Tribe*/ Xingu*/ Yup'ik/ Yupik/ Zuni/"African continental ancestry group"/"African continental ancestry group"/ "Asian continental ancestry group"/"Health Services, Indigenous"/"Oceanic ancestry group"/"arctic regions"/"ethnic groups", "HPV", "Human Papillomavirus", "Papillomavirus", "HPV 18" , "HPV*", "Qualitative", "awareness", "barriers", "HPV vaccine", "vaccine*". The search was tailored as per the design of individual databases.

In the search for published studies, the reviewers made use of facilities where the option was given to run 'related' searches, where similar studies are automatically identified. The

bibliography of each article was scanned manually for possible additions to the search. The titles and abstracts were screened by both reviewers independently to assess eligibility, with those considered relevant by either investigator advancing to a full-text review. The initial search prioritized first-hand experiences, however, a few studies included perspectives from health care workers that provided valuable insights into patient experiences. The decision was made to include these studies. The investigator pair fully screened articles to identify studies that fulfilled the following criteria:

- The study focused on the knowledge, views, experiences and barriers faced by women and/or health care workers of Indigenous identity regarding HPV vaccinations.
- Findings contained personal illustrations or first-person accounts of HPV vaccine knowledge and experiences.
- The study was qualitative or mixed methods (with clear qualitative examples)
- HPV vaccination was the phenomenon of interest
- The study was available in English
- The study was available in hardcopy or in downloadable form
- The study was published prior to 6th January, 2021

Exclusion criteria

- Based only on HPV infections and associated cancers
- Quantitative only studies

While efforts were made to decrease publication bias, the reviewers recognize that limiting the search to the English language could result in loss of data in other Native languages. Additionally, the inclusion of all grey literature could have provided additional findings for the study and decreased possible impacts of publication bias.

Critical Appraisal

There are various validated tools for appraisal of studies; this review employed the JBI (Joanna Briggs Institute) System for the Unified Management, Assessment and Review of Information (SUMARI) critical appraisal tool (Supplementary file 2). This tool includes questions regarding congruity between research philosophies, methodologies and analysis as well as findings and researcher positionality.

Data Extraction and Synthesis

Data were extracted in two phases. The first phase utilised the JBI data extraction tool for all studies, which includes study characteristics, such as location and main findings. For the second phase, the reviewers comprehensively extracted identified findings from each of the included studies. These findings were uploaded to JBI SUMARI and each reviewer independently scored the findings as "Credible", "Not Supported" or "Unequivocal"; the scorefor each finding was based on inter-reviewer agreement. The synthesis of findings was done manually by reviewers, which included writing all findings on a white board and identifying common phrases, themes and concepts. Common themes were grouped, with connections between other themes explored in the context of the HPV vaccinations in an Indigenous community. These categories were then transferred from the white board to the JBI SUMARItool and each individual finding was placed within the appropriate category. Finally, the reviewers placed each category within overarching synthesised findings, which reflected the findings from each included study.

Results

The literature search returned 2834 records, of which 969 were duplicates, leaving 1865 records after excluding duplicates. After title and abstract screening against established inclusion and exclusion criteria, 11 articles progressed to full-text review. Of the 11 potentially eligible papers, 5 fully satisfied the inclusion criteria (Figure 1). The inter-reviewer appraisal score was

8, indicating a high level of agreement between reviewers (Table 2). One study did not have a strong appraisal according to the criteria of the Qualitative Assessment and Review Instrument of method of quality appraisal, however the reviewers felt that the findings presented in the paper substantially added to the literature included in the review and did not exclude any studies on the basis of appraisal alone (Supplementary file 3). Only the authors of one article included a reflexive stance and positionality statement to identify and consider author subjectivity and impact on the creation of their findings. The lack of reflexivity in qualitative publications has recently been flagged as an area of concern to be addressed and considered by all researchers engaging in qualitative research due to the inseparable relationship between researcher subjectivity and qualitative findings (3, 4).

Studies were conducted in three countries: with Shipibo-Konibo communities in Peru; First Nations leaders, elders and health service directors in Canada; and Alaskan Native, American Native and Northern Plains American Indian communities in the United States (Table 3). Reviewers extracted 58 findings from the included articles and generated a table with each finding, illustration, and score (Supplementary file 4). The collaborative review process and synthesis of findings resulted in 17 categories, providing an appropriate base for meta-aggregation. Three overarching synthesized findings resulted from the meta-aggregation, with reviewers in agreement of all decisions (Figure 2).

Reasons for acceptance

Many findings in this review reflect parental or caregiver reasonings for why they had either previously pursued HPV vaccination for their daughter or why they wanted to after discussing the vaccine in the various projects and interventions. Parents identified vaccine use as a mechanism for and result of prioritising disease prevention (5-8). One mother identified access to vaccines as a privilege that she did not have when she was younger (7). Findings from two

studies suggested that prioritisation of disease prevention was related to the belief that one's daughter is susceptible to HPV (5, 7):

> *"Yes, I too said that with [my daughter] when she was little. 'Ay, I don't want them to vaccinate her because she will cry.' But later I thought, 'I'm wrong.' Look, it's okay that she cries. Crying is not going to kill her. It would be worse if a disease got her." (5)*

Personal experience with cancer was an important reason for acceptance among participants (6-8), many discussed a family history of cancer as a concern in terms of their child or grandchild's health: *"For me, having a strong history of all kinds of cancers in my family, one less cancer – the vaccine could protect my daughter from at least that"* (7). Wider support from schools, communities and families was highlighted as facilitating vaccine acceptance among participants (5, 8). Schools in particular were identified as a place for potential education initiatives due to the pre-existing supportive relationships between students (9). Additionally, guidance from health professionals increased vaccine acceptance among participants (5, 6), helping to provide more information or reassurance to parents or children who previously had apprehensions:

> *"At first [I] was worried because ... [I] didn't understand why [the health workers] would give her the vaccine at this age. After they explained it, [I] felt happy...that [my] daughter had received it, that she was chosen to have the vaccine." (5)*

Correct knowledge and a good foundational understanding of the HPV vaccine was another reason for acceptance (7). At the completion of focus groups, researchers from one project asked participants if they would get their children vaccinated after having discussed it in more depth and the majority of parents agreed they would (7). One participant shared that her daughter had done her own research on the vaccine and was eager to get it (7). While this

daughter had made the decision on her own, some parents, particularly mothers, discussed the necessity of parental approval prior to acceptance of the vaccine (6, 7):

> *"You know, it's like, it seems like a lot of people are saying it's their decision but in a way you know, it is up to the parent. Like you said, you can't bring them kicking and screaming, but if I felt that, if I felt so strongly about it, which I'm not sure that I do at this point, if I felt so strongly, yeah I'd bring 'em kicking and screaming, just like any other vaccine." (6)*

Reasons for hesitancy

Related to vaccine acceptance, reasons for vaccine hesitancy was another synthesized finding in this review. Both general mistrust in healthcare systems (5-8) and in vaccines (7) contributed to vaccine hesitancy for participants. Mistrust in healthcare systems reflected the history of maltreatment among Indigenous peoples and a lack of trusting relationships with current systems: *"Over my lifetime I've heard stories about Alaska Natives being used as guinea pigs and being vaccinated without their knowledge. And obviously you guys are trying to inform, but I've heard stories"* (7). Indigenous health care providers were hesitant to vaccinate as well, with one worrying that the vaccines were *"not natural… they are more chemicals given by the government to hurt us"* (8). Other participants were weary of vaccine provider abilities, worrying that the vaccine may be placed incorrectly or that a trainee would be administering the vaccine (5). One participant highlighted the importance of screening and education, providing insights into her rationale for avoiding the HPV vaccine:

> *"It goes back to vaccine versus screening, that sort of thing, you know what I mean? I think that because of the way I think, on a more natural level I don't trust drug companies, I don't trust most drugs, or any really. Um, vaccines have side effects … this is a new vaccine, we don't know what any long-term side effects are to it…I think*

> *I would go more for the screening and educating my child about how HPV is transmitted and not just HPV but other … sexually transmitted diseases. I think we need to teach our children, especially our daughters, how to listen to their bodies, you know, pay attention to their bodies, take responsibility for that." (6)*

Beliefs that research had not been conducted with regards to vaccine safety or efficacy, demonstrated the inaccessibility of research findings for the included communities (7, 9). Similarly, a lack of correct knowledge about the HPV vaccine created hesitancy for participants (6-9). Examples of incorrect knowledge among participants included that the vaccine could cause cancer or other diseases, that it was unavailable for men and that you had to be younger than 18 to receive it: *"If you got the shot you might get [HPV]. So, I was kinda nervous…I didn't want my niece to have a chance at getting that, so we didn't finish it"* (9). Several parents acknowledged that they had limited knowledge and wanted more education so that informed decisions were easier to make and they could help spread awareness to their families (9). Indigenous health workers in one study specifically identified education for parents as the first step necessary for informed vaccination decisions (9).

Structural healthcare barriers were discussed by both participants and Indigenous health workers in terms of limited resources (9). Limited vaccine endorsement from health workers was highlighted by participants: *"Doctors should recommend it more, cause I don't think I ever heard about it until I was 23"* (9). Patients additionally discussed long waiting times for appointments, healthcare provider shortages and restricted appointment lengths. Indigenous health workers identified the need for a systematic approach to result in increased uptake in communities, suggesting the possibility of working with clinic pharmacies to provide vaccine education (9).

One paper discussed the stigma associated with sexual behaviours as potential rationale for hesitancy among community members, describing the local narrative around HPV: *"I've heard my friends say, HPV is what dirty people get"* (9). Another participant from the same study discussed how fathers could be a barrier to vaccination because they may perceive vaccination approval as endorsement for promiscuous behaviour (9).

Areas for improvement

Through discussions around the HPV vaccine, participants from four of the included studies (5, 6, 8, 9) identified areas that would help improve vaccine understanding, and ultimately, vaccine uptake. A commonly identified area for improvement was the need for targeted awareness initiatives for particular groups within communities, including vulnerable populations (8), community-wide programs (outside of school systems) (8) and healthcare workers (9). As one Indigenous healthcare worker noted:

> *"For us to get out there and reach these people, we have to know what we are talking about…We need to be educated on it before we can take it and present it to people in our communities." (9)*

Further, participants discussed how current initiatives are often impersonal and detached from an individual's health: *"Doctors just throw stuff at us, so many papers [brochures]"* (8). The importance of culturally appropriate awareness initiatives, preferably in verbal rather than written form, and ideally available in Native languages was identified as important by community members (8, 9). Likewise, participants called for extended education practices to include whole families and communities, underscoring the importance of male voice and understanding in HPV conversations: *"I would not have any problem and would not be worried if they assured me, gave me good information and that person was trustworthy, and the information was also given to my husband"* (5).

Some participants felt that current practices, specifically age recommendations, should be re-considered (5, 6, 8). Many mothers shared their beliefs that current recommendations are too young for vaccination against a sexually transmitted infection, identifying a large gap in time before their children become sexually active (6). Within the same discussion, other mothers identified similarities between the HPV vaccine and birth control, contemplating that if a child brings up birth control it often indicates that they need it because they are having sex, at which point HPV prevention via vaccination might be too late (6). Additionally, one mother mentioned the possibility of sexual exposure at an early age, outside of one's control, where prevention at an early age would be key (8). The variance in beliefs and understandings of age recommendations highlights the importance of community collaboration in establishing health guidelines for each individual community. The possibility of incorporating the HPV vaccine with other infant vaccinations was also discussed:

> *"It would be better if it were the same as the rest of the vaccines they give to the newborns, at three months, six months, four months. I'd prefer it more if it was like that, so that it would be more effective, just like the other vaccines. And so that there would be a way to keep track, like the other [vaccine record] cards. It would be the same and there it could integrate into that group of vaccines." (5)*

Leveraging discussions around HPV vaccination as a chance to strengthen mother or carer communication with children was discussed as important. Some participants were disappointed when they had learned that their children or grandchildren had already received the vaccine, identifying a loss of opportunity to establish and foster openness between generations around protecting one's health (8). Other participants felt that strong communication was often established too late to prioritise prevention, such as vaccination (6). Many participants took the opportunity to discuss HPV vaccination, bodily autonomy and responsibility simultaneously with their children:

"I left it up to the two oldest ones. I left it up to them. Sat down, got as much information material as possible in regards to the whole HPV. Went through the family history with'em, between the aunts and both sides of the family and which ones have cancer so the likelihood. You know, so, the whole DNA thing…. So my daughter who's 17 years old now, she's a smart girl, I told her this is your body and I'm not gonna to make that decision for you. Here's the information, you know, read up, when we go to the doctor you know, for the next time, talk with them, ask as many questions as you want, and then it's your judgment." (6)

Discussion

Previous works have highlighted that vaccine-decision making is not a straightforward process with various factors impacting an individual's decision (10); such as, perception of disease risk, vaccine risk, vaccine safety, social discourses, communication structures, knowledge and healthcare professional recommendation (1, 2, 11, 12). The aim of this systematic review was to explore the knowledge, beliefs, attitudes and firsthand experiences of global Indigenous populations regarding HPV vaccinations. The findings represented in the conceptual model of reasons for vaccine acceptance and hesitancy among community members in the included studies, as well as areas for improvement, help generate insight into HPV vaccine uptake and understanding among the communities from the included studies. This review highlights the importance of community voice in design and delivery of awareness initiatives (5, 8, 9) as well as community co-creation of health recommendations for the HPV vaccine.

The findings collated in this review align with previous exploration of Indigenous understanding and uptake of vaccinations. Intergenerational impacts of colonisation, historic maltreatment and continuing marginalisation and oppression have significantly impacted Indigenous trust in health-related services, communications, and professionals (13-16).

Synthesised findings from the included studies highlight a commonality of mistrust in healthcare systems and vaccines (5-8), with participants describing feeling like a ‘guinea pig’ when considering vaccination (7). These feelings directly relate to historic injustices experienced by Indigenous peoples, such as medical experimentation experienced by Cree communities in Canadian residential schools (17). Health professionals have a responsibility to educate themselves prior to providing care in communities; many non-Indigenous health workers are unaware of the oppressive history of healthcare and therefore, do not properly understand potential vaccine hesitancy and mistrust they may encounter (14). Interpersonal communication with practitioners is the foundation of quality care, however it is often one of the largest barriers for Indigenous peoples (16, 18). While mistrust in healthcare is common for Indigenous communities, participants here (5, 6, 9) and elsewhere (13, 19, 20) have discussed the centrality of practitioner-patient relationship and health professional guidance in promoting vaccine acceptance. Therefore, health practitioners have an ethical obligation to respectfully engage in honest conversations with Indigenous peoples about vaccines that prioritises oral forms of education (5, 8) and increases understanding for patients. For example, clinical yarning has been suggested as a mechanism to improve clinician-patient communication with Indigenous peoples in Australia that focuses on integrating cultural communication strategies with biomedical understandings of health (21). Yarning is a traditional way of discussing important topics, with information often embedded within stories (22). The three-pronged approach to clinical yarning includes social yarns, where clinicians find common ground and develop relationships with patients; diagnostic yarns, which aim to establish the patient’s health story through a scientific lens; and management yarns, which utilise stories as a tool to increase patient understanding and develop a collaborative management approach (21).

Related to practitioner influence on vaccine acceptance, Indigenous health workers from one of the included studies brought attention to the need for increased health worker education (9). Both practitioners and patients mentioned low referral rates for the HPV vaccine in this review; increasing health worker knowledge would directly increase the frequency of vaccine recommendations and by extension, community uptake due to the influence of practitioner guidance on vaccine acceptance. Limited awareness initiatives for health workers may be related to structural barriers within healthcare systems. Similar structural barriers to those discussed in this review (9) have been documented elsewhere as obstacles to vaccination programs (5, 15, 23-25); specifically, limited resources and waiting times have been correlated with inaccessible vaccine programs. The synthesised finding of inaccessible research in this review aligns with the notion of perceived lack of testing identified among Metis communities discussing the H1N1 vaccine in Canada (13) and highlights the importance of making research accessible for communities with culturally relevant dissemination materials (26). Some participants from the included studies voiced concern or disagreement with current guidelines (5, 6, 8); co-creation of recommendations with specific communities or tailored education programming could address the misalignment of values observed here (27, 28).

Mother-daughter communication was described as an area for improvement in this review (6, 8); this reinforces how intergenerational disruptions experienced by many Indigenous communities continue to shape Indigenous health (8, 29). Prior to colonisation, sexuality was not considered shameful for Indigenous communities in Canada; adults and elders openly discussed sexual health and taught children about their bodies and sexuality was perceived as a gift to respect within oneself and with others (8, 29, 30). These significant traditions provide insight to the shift in modern discourse but also provide an opportunity for awareness initiatives to strengthen communication and relationships between elders and youth. Participants from the

included studies also emphasised the importance of centralising men in HPV conversations to increase understanding and family uptake of the vaccine.

Strengths and limitations

To the best of our knowledge, this systematic review is the first to collate qualitative perspectives of HPV vaccination among Indigenous peoples at a global level; the review was completed in accordance with all relevant protocols to ensure transparency. Highlighting areas for improvement, as discussed by participants from the included studies, is a strength of this review as it provides specific areas for future programming and policy to address. In accordance with other research, this review underscored the continuing impact of colonisation for Indigenous peoples when accessing and trusting health services, with synthesised findings providing important evidence for the work needed to address the disparities resulting from oppressive policies. Further, all but one included studied had illustrations within each of the synthesised findings, underscoring the comprehensive nature of the conceptual model (Table 5). Limitations include the low number of publications eligible for review within our inclusion criteria, which highlights the need for extended work in this field that prioritises Indigenous voice in health programming and service delivery, especially considering the increasing prevalence of oropharyngeal cancer as a result of HPV (31). Additionally, the included articles are only from three countries, emphasising the need for more research that centralises Indigenous perspectives on HPV vaccination in other countries.

Conclusion

Variance in HPV vaccine uptake among Indigenous populations is well documented (1, 2, 13). While quantitative research is essential for identifying health trends and disease spread, qualitative research is essential in exploring the stories and reasonings behind quantitative findings. Qualitative systematic reviews have the opportunity to uniquely inform policy

decisions and generate innovative solutions that successfully engage and directly benefit involved communities. Lack of correct knowledge is frequently correlated with lower vaccine uptake and while increased knowledge in communities would likely increase vaccine acceptance, the common sentiments expressed in this review of mistrust between individuals and healthcare systems (6, 7, 9) is deep-rooted in the colonial history of exploitation of Indigenous peoples. Educational programming will never have the capacity to resolve such profound issues, addressing the aspects of health systems that currently function to preserve oppressive traditions is required to provide the fundamental human right of quality care to Indigenous peoples. Papers included in this review (5, 9) have highlighted various frameworks to consider when co-creating vaccine strategies with communities, such as the Ecological approach, that acknowledge the wider influences impacting vaccine-decisions and permit the development of more holistic and community-targeted initiatives.

References

1. Lindley MC, Wortley PM, Winston CA, Bardenheier BH. The Role of Attitudes in Understanding Disparities in Adult Influenza Vaccination. American journal of preventive medicine. 2006;31(4):281-5.

2. Pritchard EN, Jutel A, Tollafield S. Positive provider interventions for enhancing influenza vaccination uptake among Pacific peoples in New Zealand. New Zealand medical journal. 2011;124(1346):75-82.

3. Braun V, Clarke V. One size fits all? What counts as quality practice in (reflexive) thematic analysis? Qualitative research in psychology. 2020:1-25.

4. Braun V, Clarke V. Reflecting on reflexive thematic analysis. Qualitative research in sport, exercise and health. 2019;11(4):589-97.

5. Clark E. Assessing Knowledge, Attitudes and Beliefs about Cervical Cancer, Human Papillomavirus and HPV Vaccine among Shipibo-Konibo Women of Peru. ProQuest Dissertations Publishing; 2014.

6. Bowen DJ, Weiner D, Samos M, Canales MK. Exploration of New England Native American Women's Views on Human Papillomavirus (HPV), Testing, and Vaccination. Journal of racial and ethnic health disparities. 2014;1(1):45-51.

7. Toffolon-Weiss M, Hagan K, Leston J, Peterson L, Provost E, Hennessy T. Alaska Native parental attitudes on cervical cancer, HPV and the HPV vaccine. International journal of circumpolar health. 2008;67(4):363-73.

8. Henderson RI, Shea-Budgell M, Healy C, Letendre A, Bill L, Healy B, et al. First nations people's perspectives on barriers and supports for enhancing HPV vaccination: Foundations for sustainable, community-driven strategies. Gynecologic oncology. 2018;149(1):93-100.

9. Schmidt-Grimminger D, Frerichs L, Black Bird AE, Workman K, Dobberpuhl M, Watanabe-Galloway S. HPV Knowledge, Attitudes, and Beliefs Among Northern Plains American Indian Adolescents, Parents, Young Adults, and Health Professionals. Journal of cancer education. 2013;28(2):357-66.

10. Boerner F, Keelan J, Winton L, Jardine C, Driedger SM. Understanding the interplay of factors informing vaccination behavior in three Canadian provinces. Human vaccines & immunotherapeutics. 2013;9(7):1477-84.

11. Nguyen T, Henningsen KH, Brehaut JC, Hoe E, Wilson K. Acceptance of a pandemic influenza vaccine: a systematic review of surveys of the general public. Infection and drug resistance. 2011;4:197-207.

12. Daniels NA, Juarbe T, Rangel-Lugo M, Moreno-John G, Perez-Stable EJ. Focus group interviews on racial and ethnic attitudes regarding adult vaccinations. Journal of the National Medical Association. 2004;96(11):1455-61.

13. Driedger SM, Maier R, Furgal C, Jardine C. Factors influencing H1N1 vaccine behavior among Manitoba Metis in Canada: a qualitative study. BMC public health. 2015;15(1):128-.

14. Mosby I, Swidrovich J. Medical experimentation and the roots of COVID-19 vaccine hesitancy among Indigenous Peoples in Canada. Canadian Medical Association journal (CMAJ). 2021;193(11):E381-E3.

15. Shahid S, Teng T-HK, Bessarab D, Aoun S, Baxi S, Thompson SC. Factors contributing to delayed diagnosis of cancer among Aboriginal people in Australia: a qualitative study. BMJ open. 2016;6(6):e010909-e.

16. Shahid S, Finn LD, Thompson SC. Barriers to participation of Aboriginal people in cancer care: communication in the hospital setting. Medical journal of Australia. 2009;190(10):574-9.

17. Mosby I. Administering Colonial Science: Nutrition Research and Human Biomedical Experimentation in Aboriginal Communities and Residential Schools, 1942–1952. Histoire sociale. 2013;46(91):145-72.

18. Cass A. Sharing the true stories: improving communication between aboriginal patients and healthcare workers.(Medical Journal of Australia). JAMA : the journal of the American Medical Association. 2002;288(8):937.

19. Dempsey AF, Zimet GD, Davis RL, Koutsky L. Factors That Are Associated With Parental Acceptance of Human Papillomavirus Vaccines: A Randomized Intervention Study of Written Information About HPV. Pediatrics (Evanston). 2006;117(5):1486-93.

20. Davis K, Dickman ED, Ferris D, Dias JK. Human papillomavirus vaccine acceptability among parents of 10- to 15-year-old adolescents. Journal of lower genital tract disease. 2004;8(3):188-94.

21. Lin I, Green C, Bessarab D. 'Yarn with me': applying clinical yarning to improve clinician-patient communication in Aboriginal health care. Australian journal of primary health. 2016;22(5):377.

22. Bessarab D, Ng'andu B. Yarning About Yarning as a Legitimate Method in Indigenous Research. International Journal of Critical Indigenous Studies. 2010;3(1):37-50.

23. Paz-Soldán VA, Bayer AM, Nussbaum L, Cabrera L. Structural barriers to screening for and treatment of cervical cancer in Peru. Reproductive health matters. 2012;20(40):49-58.

24. Zuckerman S, Haley J, Roubideaux Y, Lillie-Blanton M. Health Service Access, Use, and Insurance Coverage Among American Indians/Alaska Natives and Whites: What Role Does the Indian Health Service Play? American journal of public health (1971). 2004;94(1):53-9.

25. Duvall JBS, Buchwald DMD. Human Papillomavirus Vaccine Policies Among American Indian Tribes in Washington State. Journal of pediatric & adolescent gynecology. 2012;25(2):131-5.

26. Castleden H MD, Campbell D. Embedded in to marginalized out of place: Indigenous peoples' experience of health in Canada. In: Giesbrecht M CV, editor. Place, health, and diversity: learning from the Canadian experience. New York: Routledge; 2016.

27. Batliner T, Fehringer KA, Tiwari T, Henderson WG, Wilson A, Brega AG, et al. Motivational interviewing with American Indian mothers to prevent early childhood caries: study design and methodology of a randomized control trial. Trials. 2014;15(1):125-.

28. Wilson S. Research is ceremony : indigenous research methods. Black Point, N.S: Fernwood Pub.; 2008.

29. Canada. ANoCaPPFo. Finding Our Way: A Sexual and Reproductive Health Sourcebook for Aboriginal Communities. Toronto: Aboriginal Nurses Association of Canada.; 2012.

30. Hunt S. An Introduction to the Health of Two-Spirit People: Historical, Contemporary and Emergent Issues. Prince George: National Collaborating Centre for Aboriginal Health; 2016.

31. Henry JV, GS; Brooks, JK; Abbas, FM; Bashirelahi, N. What every dentist needs to know about human papillomavirus. General Dentistry. 2021;69(2):23-7.

Figure 1: PRISMA flowchart

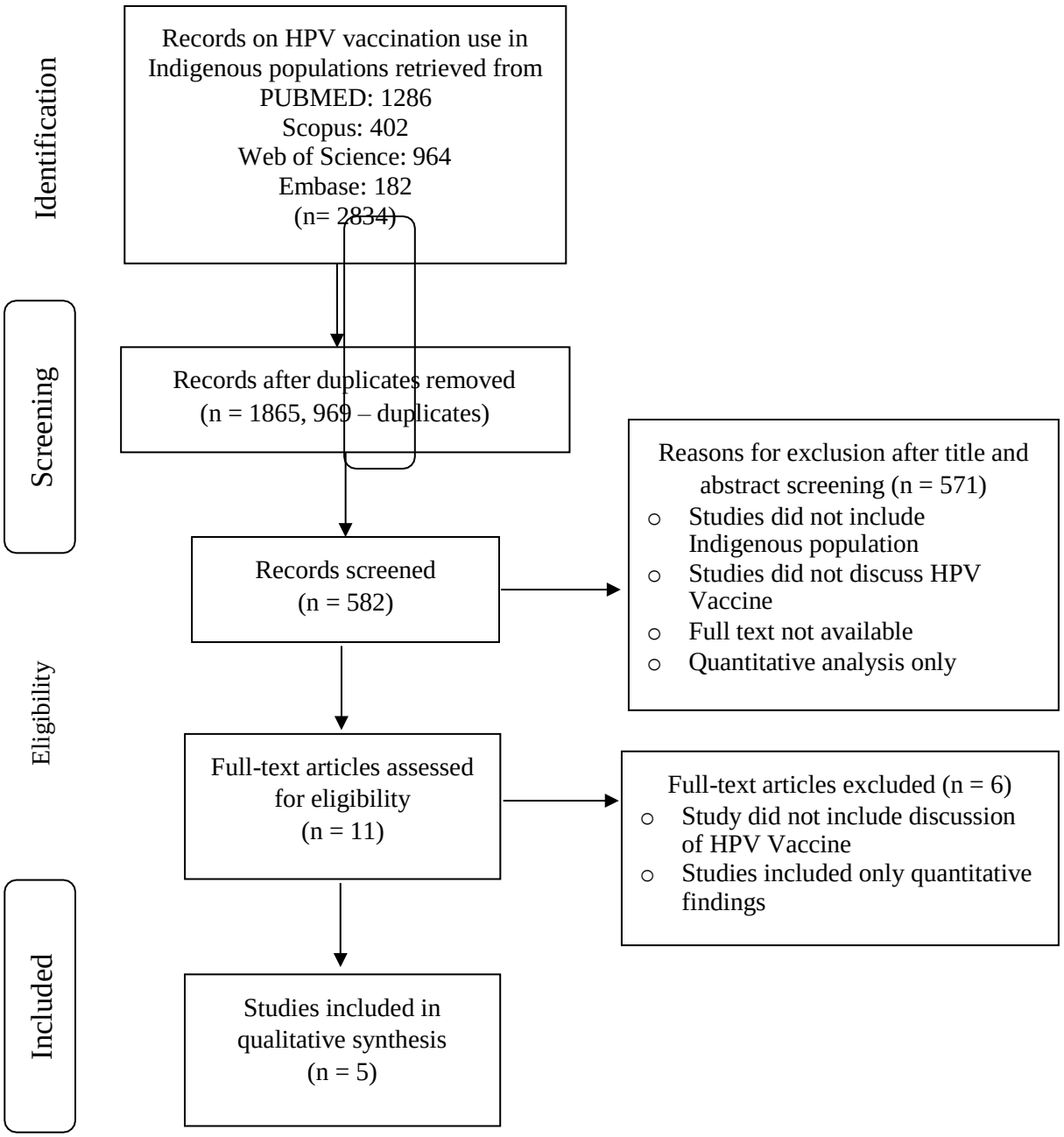


Figure 2. Conceptual model for HPV Vaccine acceptance and hesitancy among Indigenous populations.

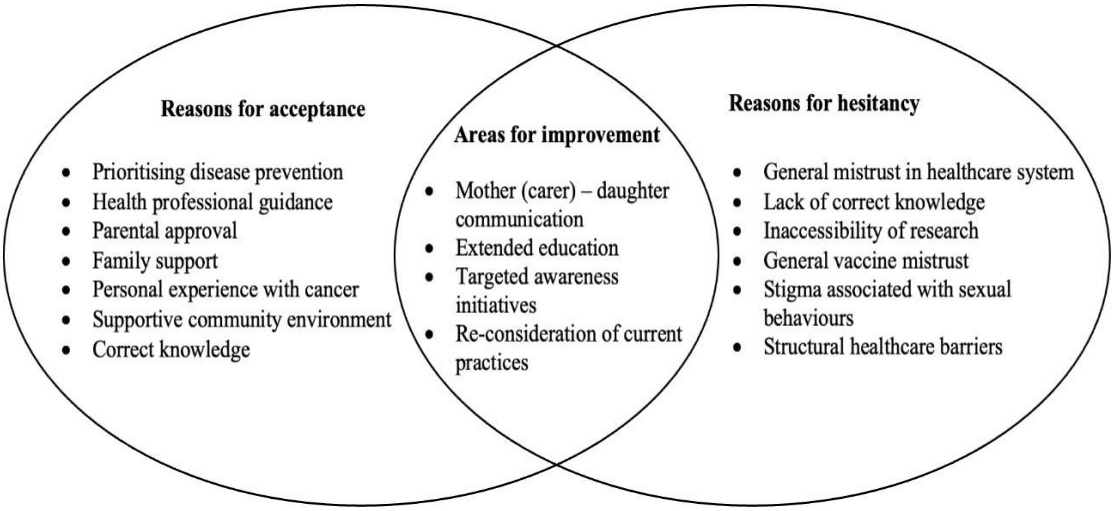


Table 1: ENTREQ Checklist

Item	Description	Reported on Page #
Aim	The objective of this systematic review was to explore the knowledge, beliefs and experiences of Indigenous populations all over the world regarding HPV vaccines.	2
Synthesis methodology	Content analysis guided initial data extraction for synthesis, and the conceptual model provided a theoretical framework to present the synthesised findings	5
Approach to searching	Pre-established search strategy which involved using terms describing the population of interest, the phenomenon we are researching as well as study designs to be included	3
Inclusion criteria	*Inclusion*: The study focused on the knowledge, views, experiences and barriers faced by women and/or health care workers of Indigenous identity regarding HPV vaccinations. Findings contained personal illustrations or first-person accounts of HPV vaccine knowledge and experiences. The study was qualitative or mixed methods (with clear qualitative examples) HPV vaccination was the phenomenon of interest. The study was available in English. The study was available in hardcopy or in downloadable form. The study was published prior to January, 2021 *Exclusion*: Based only on HPV infections and associated cancers. Quantitative only studies	4
Data sources	MEDLINE, PubMed, SCOPUS, and Web of Science databases; each search tailored per the design of individual database. In our search for published studies, we made use of facilities when given to run 'related' searches and the bibliography of each article was manually scanned for possible additions to the study	3

Electronic Search Strategy	Terms utilised for literature search included: 'HPV' 'Vaccine' 'Indigenous' 'narrative' 'story' 'qualitative' 'mixed methods'	3
Study Screening methods	Two independent researchers screened studies for inclusion in the qualitative systematic review. Titles were first reviewed, then abstracts and those considered relevant by either investigator advanced to full text review.	2 and 3
Study characteristic	See Table 3	Table 3
Study selection results	179 records were returned from initial search, 116 were excluded due to duplication, 63 shortlisted, 5 studies fully satisfied inclusion criteria.	Figure 1
Rationale for appraisal	Utilizing JBI SUMARI software, articles were appraised according to the CASP (2013) method of quality appraisal.	S2 and S3
Appraisal Items	See S2 and S3	S2 and S3
Appraisal Process	Appraisal was conducted independently by both reviewers and then findings were discussed, and consensus was required before moving forward.	4
Appraisal Results	All 5 articles were included after the appraisal because they satisfied inclusion criteria of personal illustrations	Table 6
Data extraction	All text under headings "Results" and "Conclusions," as well as all findings under the heading "Discussion" were analysed. Data was manually extracted with highlighters from printed versions of appraised articles and then imputed into the JBI SUMARI software.	Table 4, Table 3
Software	JBI SUMARI	2

Number of Reviewers	Two reviewers independently reviewed articles and extracted data. Findings were then compared, discussed and compiled.	4
Coding	Data was coded from selected articles, going line by line to search for concepts and considering the author-prescribed themes.	5
Study Comparison	All findings were individually highlighted and written on a white board and then connections were made between findings and categories were created based on similarities within and across extracted data.	5
Derivation of themes	The process of deriving themes was abductive.	5
Quotations	Table 4	Table 4
Synthesis output	Results section and Figure 2	5-10 and Figure 2

Table 2: Inter-reviewer reliability table

Study	Number of questions in agreement	Number of questions in disagreement	Score
Toffolon-Weiss et al, 2008	5	5	5
Schmidt-Grimminger et al, 2013	8	2	8
Bowen DJ et al, 2014	8	2	8
Clark et al, 2014	10	0	10
Henderson RJ et al, 2018	9	1	9
Mean			**8**

Table 3: Characteristics of Included Studies

Study	Methods for data collection and analysis	Country	Phenomena of interest	Setting/context/culture	Participant characteristics and sample size	Description of main results
Bowen DJ WD. 2014.	Recruitment: flyers in public places, word of mouth, referrals from social groups Five focus groups, 90-minute sessions. Recording sessions and transcribing Analysis: Data coded, analysed and interpreted to identify emerging themes	United States of America	Attitudes and beliefs for cancer screening practices in American Indian women	American Native/ American Indian	102 participants Age range: 18-64 years Caregivers of adolescent Native American girls (for whom HPV vaccine is recommended)	Themes: 1. Disease prevention is important 2. HPV vaccine recommendations are unclear 3. Communicating with daughter 4. Confusion about HPV testing and HPV vaccination 5. Patient-provider relationship is important 6. Medical Mistrust
Henderson RJ S-BM. 2018.	Recruitment: One day event with First nations elders and leaders, presentations, discussions and sharing circles. The discussions were recorded and transcribed. Analysis: Coding of transcriptions in NVivo 10 including a thematic analysis	Canada	Barriers and facilitators for HPV vaccinations among First Nation populations	First Nations leaders, elders and health service directors	Sample Size: 24	Themes: 1. The need for a trauma informed lens 2. Role of family and community ties 3. Adapting to a changing information landscape
Schmidt-Grimminger D FL. 2013.	Community based participant research, focus groups for qualitative data, transcription and coding of data collected Thematic analysis	United States of America	Knowledge, attitudes and beliefs related to the HPV vaccine and factors that facilitate or hinder vaccination among Alaskan Native populations	Alaskan Native groups	Sample size: 73	Themes: 1. HPV and HPV vaccine perceptions 2. Information needs and service providers 3. Barriers to HPV vaccination 4. Suggestions for improving HPV vaccination rates
Clark E. 2014.	Semi-structured interviews, thematic analysis based upon grounded theory	Peru	Knowledge, attitudes, beliefs about cervical cancer, HPV	Ucayali river basin in the Amazoni	(N=30), Women, ages 18-39, Shipibo-Konibo Indigenous,	Geographic differences in attribution of cervical cancer and importance of vaccine information for parents,

			and HPV vaccine	an province of Ucayali; Shipibo-Konibo Indigenous Women		although few women had heard of the HPV vaccine, all were in favour of their daughters receiving vaccination
Toffolon-Weiss M. 2008.	Focus groups, audiophiles and moderator notes on non-verbal behaviours; analysed with Atlas TI software	Alaska, USA	Parental attitudes on cervical cancer, HPV and HPV vaccine	Alaska Native parents from urban, hub and village communities	(N=79), all had a 9-18-year-old daughter or ward; 64 female, 15 male, age 21-61+, N=28 experience in medical setting	The majority of parents were interested in having their daughters vaccinated. Acceptance of the vaccine was primarily based on a parent's desire to protect her/his child from cancer; while reasons for refusal revolved around trust issues and fear of unknown negative consequences of the vaccine.

Table 4: Illustrations from all the included studies arranged according to synthesized findings and categories under the conceptual model

Categories	Synthesized Finding	Illustration
Reasons for acceptance	Prioritizing disease prevention	"Maybe sometime in the near future, at a young age, my daughter could become pregnant. So the virus could affect her. Better said, this age [for vaccination] is good." (Clark, 2014)
		"Yes, I too said that with [my daughter] when she was little. “Ay, I don’t want them to vaccinate her because she will cry.” But later I thought, “I’m wrong.” Look, it’s okay that she cries. Crying is not going to kill her. It would be worse if a disease got her." (Clark, 2014)
		Only a few of the women consistently engaged in preventive behaviors or commented that prevention was not important or preferable to treatment. (Bowen, 2014)
		“I see it as just part of being a mom and wanting to protect your child against cancer.” (Toffolon-Weiss, 2008)
		“For me, having a strong history of all kinds of cancers in my family, one less cancer – the vaccine could protect my daughter from at least that.” (Toffolon-Weiss, 2008)
		“I didn’t have all that privilege of getting all of those kinds of vaccines. Now that they are coming up with good kinds of things I would give my kids the privilege to get them.” (Toffolon-Weiss, 2008)
		Another theme that was mentioned by at least one parent in each community was that often sexual exposure was not under the control of the young woman, as in the case of rape, and this vaccine would offer the young woman protection from HPV. (Toffolon-Weiss, 2008)

		"I don't think it'll encourage my daughter to go out and have sex. I don't want her to have sex now. She's 14. I hope she has sex in the future and has kids and lives a normal life, but I don't think it will encourage her to go act irrationally." (Toffolon-Weiss, 2008)
		Parents appeared to view the vaccine strictly from a health-related perspective and to accept that their daughters would eventually be sexually active as they grew older and would become susceptible to HPV. (Toffolon-Weiss, 2008)
		Recognizing a complex sequence of risks that may heighten vulnerability, the participant ensured that her daughter received the HPV vaccine at school, wishing only that it had been available sooner. (Henderson, 2018)
	Health professional guidance	"At first [I] was worried because ... [I] didn't understand why they would give her the vaccine at this age. After they explained it, [I] felt happy...that [my] daughter had received it, that she was chosen to have the vaccine." (Clark, 2014)
		"I would not have any problem and would not be worried if they assured me, gave me good information and that person was trustworthy, and the information was also given to my husband." (Clark, 2014)
		"When we sat down with xxxx (daughter), and I went through thing well why are they getting the shot, … I explained to her about the virus. Well how do you get it? I said 'well it's sexually transmitted' now she picked up – on – that and wanted to discuss it with me, and then I carry on. I think she, at 9 y/o, she knows about sex… and so I explained to her about that. And, you know, I said you know 'you're 9 years old' you know. I said, you know I'm not gonna do it now, but when you get

		the shot, get the shot. She said 'No, I'll wait!' But I explained everything to her and you know, given her pediatrician explain it to her." (Bowen, 2014)
	Parental approval	"It seems to me that this vaccine, like when you see the commercials and all it's like "talk to your child". Well we don't have the opportunity to talk to our children about other things that we've had to give them. You know, it's like, it seems like a lot of people are saying it's their decision but, in a way, you know, it is up to the parent. Like you said, you can't bring them kicking and screaming, but if I felt that, if I felt so strongly about it, which I'm not sure that I do at this point, if I felt so strongly, yeah, I'd bring 'em kicking and screaming, just like any other vaccine." (Bowen, 2014)
		The majority of mothers in the Alaskan focus groups said that they alone made the decision to vaccinate their children against a disease. Some said that they made the decision in conjunction with their spouses and a few said that they involved their daughters and spouses in the decision-making. (Toffolon-Weiss, 2008)
	Family support	When asked, all but one participant said they felt their families would be supportive of the vaccine as well. One woman said it didn't matter to her if her family agreed or disagreed, that the decision to vaccinate was between her and her daughter. (Clark, 2014)
	Personal experience with cancer	"For me, having a strong history of all kinds of cancers in my family, one less cancer – the vaccine could protect my daughter from at least that." (Toffolon-Weiss, 2008)
		"I am learning a lot in these workshops. My mother died of stomach cancer, my sister of stomach cancer. I had 5 girls, and 4 of them went through breast cancer. My oldest daughter, her cancer spread. When they were

		younger I made sure they all got their needles. But, you know, I have never had a workshop like this. If I get a cold, I can fight it off. When I got those needles, I was told I was able to fight the sicknesses; it won't kill you—that is what I was told. This is really good for my grandchildren; I will take this message home to my family. I have two nurses in my family, they probably know about it, but this is a really good thing I am still learning… [*speaking in Cree] *I was worried the white people would not take care of us, but they have so far [group laughs]. We need to talk to young ladies about how to take care of themselves." (Henderson, 2018)
	Supportive community environment	"There are anti-bullying programs…and there are cultural programs; some kids are brave and some are afraid of getting immunized, but all the children support each other." (Henderson, 2018)
		This supportive environment among youth receiving the vaccine was encouraged in some communities by celebrating the event of vaccination itself, with a meal and acknowledging the support that youth provided to one another. (Henderson, 2018)
		Young adults also recommended education in the school and recommended beginning in junior high or younger, and made suggestions such as, "have some nurses come in [and] do different classes." (Schmidt-Grimminger, 2013)
		Parents also suggested education during health classes but also noted the possibility of vaccinating at the school, "if they get the shot in school, the first month that school started, by the time school was out those kids would be completely through." (Schmidt-Grimminger, 2013)

	Correct knowledge	“My daughter is 17, and she’s the one who went out, did her research on the shot, and she’s been patiently waiting for it.” (Toffolon-Weiss, 2008)
		When asked in a “round-robin” fashion at the end of the focus group whether they would get their children vaccinated, the majority of parents answered affirmatively. (Toffolon-Weiss, 2008)
Reasons for hesitancy	General mistrust in healthcare system	"Well, they could place the vaccine badly, or they could make an error about the medicine, or the person who places it could be a trainee." (Clark, 2014)
		"You know, …when they come to me, you know, I just, I don’t like putting any foreign objects, substance in my body, that’s man made…I don’t know, I just can’t, I can’t do it. When it comes to the innovation shots with the kids, you know, some of them I think it’s, like small pox. come on, people, …why are you shooting my kid up with this live virus, what’s the matter with you? Then the whole circumstances, you know, …well gee, guess what? you have the innovation right there, so why put my kid, even though the risk factor’s so low but, you know, they could be the 1 in you know 100,000 deaths or could come down with, now with some of the shots they are saying that it has to do with autism later in life. Participant—The mercury? I had a very hard time with that also. Especially with my son because it’s, the rates are higher in boys. I had a really, I held off for longer than you’re supposed to, because I just didn’t feel comfortable." (Bowen, 2014)
		"It’s a little bit off what you’re just asking us. It goes back to vaccine versus screening, that sort of thing, you know what I mean? I think that because of the way I think, on a more natural level I don’t trust drug companies, I don’t trust most drugs, or any really. Um,

		vaccines have side effects and could cause, this is a new vaccine, we don't know what any long-term side effects are to it. So, I think in that way, if I had a daughter that was that young now. I have, my daughter's 33, 34. But SHE has a daughter. I think I would go more for the screening and educating my child about how HPV is transmitted and not just HPV but other …sexually transmitted diseases. I think we need to teach our children, especially our daughters, how to listen to their bodies, you know, pay attention to their bodies, take responsibility for that." (Bowen, 2014)
		"Over my lifetime I've heard stories about Alaska Natives being used as guinea pigs and being vaccinated without their knowledge. And obviously you guys are trying to inform, but I've heard stories." (Toffolon-Weiss, 2008)
		One health director who was herself FN had not approved the HPV vaccine for her own daughter, believing at the time that vaccines are perhaps "not natural, that they are more chemicals given by the government to hurt us". This perspective highlights mistrust in health systems even among Indigenous providers, some who may feel that health promotion is often impersonal and uninvested in one's actual health, where "doctors just throw stuff at us, so many papers [brochures]." (Henderson, 2018)
	Lack of correct knowledge	"It's, I mean, there are percentages, there's risk and everything, but that adult person, as to whether you want to take that risk, or you don't… or you run a risk of em getting the disease. That's what it comes down to me. It's the risk of the drug against the risk of the disease itself." (Bowen, 2014)

	"I lean towards it, it sounds like a good thing. I just wish there was a lot more information, and I wish there was a lot more information from somebody other than Merck." (Toffolon-Weiss, 2008)
	"The health center sent out a notification and a consent form, and they listed the benefits and risks…and I paid more attention to the risks, and I decided not to allow her to be vaccinated, because as a parent I needed to do what was best for my children." (Henderson, 2018)
	Several parents noted that they did not feel knowledgeable, but wanted information so they could make informed decisions in order to educate their daughters and nieces about HPV. (Schmidt-Grimminger, 2013)
	Several parents revealed a perception that the vaccine was thought to potentially cause cancer or disease and that HPV and cervical cancer were hereditary and had a genetic cause. (Schmidt-Grimminger, 2013)
	"What I've heard is the stuff on the commercials, you know. Get your shot…oh, you're 18…I missed that shot. I'm not 18 no more." (Schmidt-Grimminger, 2013)
	Within the young adult and tribal healthcare providers, there was confusion about whether or not HPV was something men could get. (Schmidt-Grimminger, 2013)
	"if you got the shot you might get it. So I was kinda nervous…I didn't want my niece to have a chance at getting that, so we didn't finish it." (Schmidt-Grimminger, 2013)
	Tribal healthcare providers discussed the parent barrier as a need to provide more education, "it's got to be the number one thing, is letting them know what it is and how they can get the help and everything about it. The

		education is that first step." (Schmidt-Grimminger, 2013)
	Inaccessibility of research	"I don't like to be the first to use a new vaccine. That makes me uncomfortable that it hasn't been used by a lot of people yet. Some side effects may turn up that they don't know about until they vaccinate a whole bunch of kids." (Toffolon-Weiss, 2008)
		"I still think people still have a lot of questions, they are really unsure. A question I had was how long did they do research on that vaccine to determine the safety." (Schmidt-Grimminger, 2013)
	General vaccine mistrust	"Well, just like she was saying, there's that risk of introducing something into your body that you probably wouldn' t have contracted, but then you introduce it and you get it. That's my fear." (Toffolon-Weiss, 2008)
		"Over my lifetime I've heard stories about Alaska Natives being used as guinea pigs and being vaccinated without their knowledge. And obviously you guys are trying to inform, but I've heard stories." (Toffolon-Weiss, 2008)
		"I also learned about autism. And I started to read about vaccinations…was getting scary about getting these vaccinations." (Schmidt-Grimminger, 2013)
	Stigma associated with sexual behaviors	However, participants did note there were negative perceptions about HPV in the community that could be a potential barrier. One participant noted, "I've heard my friends say, HPV is what dirty people get." (Schmidt-Grimminger, 2013)
		"The father will be the barrier, because he thinks it gives them the go ahead to be promiscuous." (Schmidt-Grimminger, 2013)

	Structural healthcare barriers	Resource issues within the clinic were also identified in both the parent and IHS focus groups. Parents noted providers not recommending the vaccine or lengthy waiting times to get an appointment. IHS providers also recognized resource constraints within the clinic. For example, several participants noted concerns with the amount of time they had with patients and shortages of providers. (Schmidt-Grimminger, 2013)
		"Doctors should recommend it more, cause I don't think I ever heard about it until I was 23." The IHS healthcare providers said that a more systematic approach was needed to increase the uptake of the vaccine. For example, they noted the possibility of working with the clinic pharmacy to provide counselling and the vaccine. (Schmidt-Grimminger, 2013)
Areas for improvement	Mother (carer) – daughter communication	Native women indicated that by the time that good mother–daughter communication about sexual issues occurred, it would be too late, as exposure would have already occurred. (Bowen, 2014)
		"I left it up to the two oldest ones. I left it up to them. Sat down, got as much information material as possible in regards to the whole HPV. Went through the family history with'em, between the aunts and both sides of the family and which ones have cancer so the likelihood. You know, so, the whole DNA thing…. So my daughter who's 17 years old now, she's a smart girl, I told her "this is your body and I'm not gonna to make that decision for you. Here's the information, you know, read up, when we go to the doctor you know, for the next time, talk with them, ask as many questions as you want, and then it's your judgment." (Bowen, 2014)
		"When we sat down with xxxx (daughter), and I went through thing well why are they getting the shot,… I

		explained to her about the virus. Well how do you get it? I said 'well it's sexually transmitted' now she picked up – on – that and wanted to discuss it with me, and then I carry on. I think she, at 9 y/o, she knows about sex… and so I explained to her about that. And, you know, I said you know 'you're 9 years old' you know. I said, you know I'm not gonna do it now, but when you get the shot, get the shot. She said 'No, I'll wait!' But I explained everything to her and you know, given her pediatrician explain it to her." (Bowen, 2014)
		Some speakers were disappointed to learn after the fact that their grandchild had been vaccinated, sensing that they had lost an opportunity to discuss with the youth issues related to sexual intercourse, to foster the kind of openness between generations believed to be protective of health. These participants believed that health providers or teachers could provide some education. (Henderson, 2018)
	Extended education	"I would not have any problem and would not be worried if they assured me, gave me good information and that person was trustworthy, and the information was also given to my husband." (Clark, 2014)
	Targeted awareness initiatives	Those in the child welfare system were described as having few supports to learn anything about their own bodies, let alone to have anyone following up whether they receive the HPV vaccine within school-based programs. (Henderson, 2018)
		Others could appreciate that it might be difficult from a school's perspective to educate in detail all families about HPV, but these speakers proposed that school-based programs alone were not entirely effective, and instead require outreach to older generations as well, "to get the word out." (Henderson, 2018)

		The importance of verbal forms of education was among the strongest themes, underscoring that prevention without relationships would be unlikely to improve HPV vaccine uptake or related health outcomes. (Henderson, 2018)
		"For us to get out there and reach these people, we have to know what we are talking about…We need to be educated on it before we can take it and present it to people in our communities…." (Schmidt-Grimminger, 2013)
		The groups mentioned education through venues such as health fairs, radio announcements, and posters. The tribal and IHS healthcare providers discussed the importance of culturally appropriate education and outreach. For example, the tribal healthcare providers noted that some materials should be in their native language (Lakota) in order to successfully conduct outreach to elders of the community who are important opinion leaders in their community. Similarly, the IHS providers noted that they could provide more educational materials in the clinic but stated that it would be better if they were culturally specific to the Northern Plain. (Schmidt-Grimminger, 2013)
	Re-consideration of current practices	"It would be better if it were the same as the rest of the vaccines they give to the newborns, at three months, six months, four months. I'd prefer it more if it was like that, so that it would be more effective, just like the other vaccines. And so that there would be a way to keep track, like the other [vaccine record] cards. It would be the same and there it could integrate into that group of vaccines." (Clark, 2014)
		Many women expressed the idea that 9 years old was too young to get a vaccine that protected against a

	sexually transmitted disease because the child was still a few years away from having sex, and it was at that later point that the decision should be made about vaccination or not. (Bowen, 2014)
	Some women pointed out that by the older age, it might be too late, and that if girls had to bring up a vaccine when they were considering having sex, it would operate the same as birth control in that if a child brings up birth control, it means that she is having sex and needs it. (Bowen, 2014)
	Recognizing a complex sequence of risks that may heighten vulnerability, the participant ensured that her daughter received the HPV vaccine at school, wishing only that it had been available sooner. (Henderson, 2018)

Table 5: Conceptual model distribution of studies

Studies	Reasons for Acceptance	Reasons for Hesitance	Areas for improvement
Toffolon-Weiss et al, 2008			
Schmidt-Grimminger et al, 2013			
Bowen DJ et al, 2014			
Clark et al, 2014			
Henderson RJ et al, 2018			

*Highlighted boxes show the contribution of a study to a particular ecological level.

Table 6: Appraisal of included studies

Citation	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10
Bowen DJ WD. 2014.	U	Y	Y	Y	Y	N	N	Y	U	Y
Henderson RJ S-BM. 2018.	Y	Y	Y	Y	Y	N	U	Y	Y	Y
Schmidt-Grimminger D FL. 2013.	Y	Y	Y	Y	Y	N	N	Y	U	Y
Clark E. 2014.	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Toffolon-Weiss M. 2008.	U	Y	Y	N	U	N	N	N	U	N
%	60.0	100.0	100.0	80.0	80.0	20.0	20.0	80.0	40.0	80.0

“Those who stop dreaming are lost”

–Australian Aboriginal Proverb