THE BURDEN OF CANCER AND ITS DISTRIBUTION AND CONSEQUENCES FOR AUSTRALIA: EVIDENCE FROM HEALTH ECONOMIC EVALUATION AND ADVANCED STATISTICAL MODELLING

A Thesis submitted by

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Abstract

Cancer is expected to rank as the most significant global public health problem and a leading cause of death and illness in the world in the 21st century. The burden of cancer is rapidly increasing globally, including Australia. The responses to this growing burden of cancer have been limited owing to a poor understanding of the long-term burden of cancer and its consequences. The overarching aim of this thesis is to investigate the burden of cancer on patients, households, as well as on society over time. This thesis also aims to generate evidence for health policymakers, who make nationwide cancer control and management decisions on cancer prevention (e.g., cancer vaccination) and cancer treatment programs. This thesis has examined the burden of cancer using a geographical lens, including regional, rural, and remote areas in Australia. To accomplish this aim, five empirical studies for assessing the impact of the cancer burden in terms of long-term cancer outcomes (an incidence-based approach); health status burden, chronic comorbid conditions, productivity-related work disability (mixed-longitudinal approach); and the economics of cancer vaccination (economic evaluation) have been conducted.

This thesis is constructed using three main themes of study including 'understanding the challenges of cancer outcomes', 'the long-term cancer burden (i.e., health status burden, chronic comorbid conditions, productivity-related work disability, and its consequences)', and 'evaluation of cancer vaccination' in the context of Australia. These inter-related studies result in a thesis by publication. These studies are constructed based on a quantitative approach, using health economic evaluation and advanced statistical modelling. The thesis is based on six articles, national health data sets are utilised for the first article, three of them (Articles 2 to 4) being mixed-longitudinal nature survey-data driven from the Household Income and Labour Dynamics in Australia survey, and two of them (Articles 5 and 6) based on national and international contexts and published data sources related to cancer and health economics modelling.

The findings of this thesis have been theorised inductively, which means the analytical exploration has been data-grounded, rather than theory-dictated. In this thesis, every finding is underpinned by a suitable theoretical framework. Three inductively generated theories are adopted: social conflict theory, stress-coping theory, and portfolio theory perspectives.

The thesis revealed that all of these factors (e.g., cancer incidence, hospitalisation, cancer-related mortality, and burden of cancer) increased significantly over the period. Furthermore, survival inequality was most pronounced for cervix, prostate, melanoma, Non-Hodgkin Lymphoma, and breast cancers. Additionally, socio-economically disadvantaged people were more likely to bear an increasing cancer burden in terms of incidence, mortality, and death. The findings of the thesis showed that approximately 36% of cancer patients had an initial high health status burden in 2013, which had declined significantly to 21% by 2017. Adequate levels of sleep, physical activity, social support, and higher economic status were significantly associated with improving health status.

This thesis revealed that 61% of cancer patients experienced at least one chronic condition over the period, and 21% of patients experienced three or more chronic conditions. An inadequate level of physical activity, patients who suffered from extreme health burden or moderate health burden, and patients living in the poorest households were significantly associated with a higher risk of chronic comorbid conditions. This research also found that approximately 50% of cancer patients had experienced with long-term productivity-related work disability, 18% of patients had experienced extreme work disability, which was more pronounced with the magnitude of their health status burden. Finally, cancer prevention program (cancer vaccination) demonstrated '*good value for money*', if the adopted vaccination strategies could accomplish a high vaccination coverage and provide protection. With a continued assessment of the potential vaccine properties as well as vaccine delivery and scale-up strategies, the two-dose *9vHPV* vaccine would provide significant health and economic benefits for preadolescents and society.

This thesis provides a better understanding of the challenges of cancer outcomes and long-term consequences on health status burden, chronic comorbid conditions, and productivity-related work disability, and has provided an evaluation of cancer vaccination for preventing cancer-related infections, along with contributing to the ongoing debate of cancer research. The findings are also significant for health care providers, including physical therapists and oncologists, who must manage the unique problems that challenge this population and who should advocate for prevention and evidence-based interventions that incorporate comprehensive social supports. The findings of this thesis will contribute to the decision-making process regarding the prevention of cancer illness, better outline the management of a sequelae course of treatment for cancer survivors, both of which aim to reduce the long-term burden in Australia.

Certification of Thesis

This thesis is entirely the work of Md Rashidul Alam Mahumud except where otherwise acknowledged, with the majority of the authorship of the papers presented as a Thesis by publication undertaken by the student.

The work is original and has not previously been submitted for any other award in this University or any other, except where acknowledged.

Student and supervisors′ signatures of endorsement are held at USQ.

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Principal Supervisor — Date

Professor Jeff Dunn — *13/02/2020*

Associate Supervisor — Date

Professor Jeff Gow — *13/02/2020*

Associate Supervisor — Date

Statements of Contributions

The articles produced from this study were a joint contribution of the researchers. The details of the scientific contribution of each researcher are provided below:

- **Study 1: Understanding the challenges of cancer outcomes: Incidence, mortality, hospitalisation and associated burden**

Article I:

Rashidul Alam Mahumud*, Khorshed Alam, Jeff Dunn, Jeff Gow. Emerging cancer incidence, mortality, hospitalisation, and associated burden among Australian cancer patients, 1982-2014: An incidence-based approach in terms of trends, determinants and inequality. *BMJ Open* 2019; 9(12): e031874. (Quartile-1 ranked; Impact Factor: 2.376; SJR = 1.321; SNIP = 1.145; Publisher: BMJ Publishing Group).

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The overall contribution of ***Rashidul Alam Mahumud*** was 75% to the concept development, data extraction, analyses, interpretation, drafting and revising the final submission; ***Khorshed Alam, Jeff Dunn*** and ***Jeff Gow*** contributed to the concept development, editing and providing important technical inputs by 10%, 10% and 5%, respectively.

- **Study 2: Cancer burden: Long-term health status and consequences**

Article II:

Rashidul Alam Mahumud*, Khorshed Alam, Jeff Dunn, Jeff Gow. The impact of lifestyle risk factors, life satisfaction and chronic exposure on changing in longitudinal health status burden among Australian cancer patients, 2013-2017. *BMJ Open* (under review). (Quartile-1 ranked; Impact Factor: 2.376; H-Index: 69; SJR = 1.321; SNIP = 1.145; Publisher: BMJ Publishing Group).

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- **Study 3: Cancer burden: Long-term chronic comorbid conditions and consequences**

Article III:

Rashidul Alam Mahumud*, Khorshed Alam, Jeff Dunn, Jeff Gow. The burden of chronic diseases among Australian cancer patients: Evidence from a longitudinal exploration, 2003-2017. *PLoS ONE* 2020*;* 15(2): e0228744 (Quartile-1 ranked, Impact Factor: 2.392; H-Index: 268; SJR = 1.100; SNIP = 1.123; Publisher: Public Library of Science).

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- **Study 4: Cancer burden: Impact of long-term productivity-related work disability and consequences**

Article IV:

Rashidul Alam Mahumud*, Khorshed Alam, Jeff Dunn, Jeff Gow. The changing relationship between health burden and work disability of Australian cancer survivors, 2003-2017: Evidence from a longitudinal survey. *BMC Public Health* 2020; 20 (548):1-14 (Quartile-1 ranked, Impact Factor: 2.567; H-Index: 117; SJR = 1.382; SNIP = 1.342; Publisher: Springer Nature).

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- **Study 5: Prevention strategy of cancer program: Economic evaluation of cancer vaccination**

Article V:

Rashidul Alam Mahumud*, Khorshed Alam, Syed Afroz Keramat, Gail Ormsby, Jeff Dunn, Jeff Gow. Cost-effectiveness evaluations of the 9-Valent human papillomavirus (HPV) vaccine: Evidence from a systematic review. *PLoS ONE* 2020; 15(6): e0233499 (Quartile-1 ranked, Impact Factor: 2.392; H-Index: 268; SJR = 1.100; SNIP = 1.123; Publisher: Public Library of Science).

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Article VI:

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These articles will be referred to by their roman numerals (I-VI) in the text.

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List of Abbreviations

AAPC	Average Annual Percentage Change
ABDS	Australian Burden of Disease Study
ABS	Australian Bureau of Statistics
ACD	Australian Cancer Database
ACT	Australian Capital Territory
AHS	Australian's Health System
AIHW	Australian Institute of Health and Welfare
ANOVA	One Way Analysis of Variance
APC	Annual Percentage Change
ASR	Age-Standardised Rate
CC	Cervical Cancer
CDC	Centres for Disease Control
CCR	Central Cancer Registry
CET	Cost-Effectiveness Threshold
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CI	Concentration Index
DALY	Disability-Adjusted Life Year
DW	Disability Weight
GBD	Global Burden of Disease
GDP	Gross Domestic Product
GLM	Generalised Linear Model
GLMM	Generalized Linear Mixed Model
GP	General Practitioner
HPV	Human Papillomavirus
HP	Helicobacter Pylori
HBV	Hepatitis B Virus
HILDA	Household, Income and Labour Dynamics in Australia
ICER	Incremental Cost-Effectiveness Ratio
IRSD	Index of Relative Socio-economic Disadvantage
IER	Index of Economic Resources
IRR	Incidence Rate Ratio
LMD	Least Advantaged-Most Advantaged Differences

LMR	Least Advantaged-Most Advantaged Ratio
LMICs	Low- and Middle-Income Countries
MET	Metabolic Equivalent of Task
NCDs	Noncommunicable Diseases
NHIP	National HPV Immunisation Program
NHMD	National Hospital Morbidity Database
NMD	National Mortality Database
NSW	New South Wales
NT	Northern Territory
OOP	Out-of-Pocket
OECD	Organisation for Economic Co-operation and Development
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QALY	Quality-Adjusted Life-Year
QLD	Queensland
RQs	Research Questions
RESET	Ramsey Ramsey Regression Equation Specification Error Test
RRR	Relative Risk Ratio
SA	South Australia
SDGs	Sustainable Development Goals
SE	Standard Error
SF-36	Short Form-36
SES	Socioeconomic Status
TAS	Tasmania
USA	United States of America
VIC	Victoria
VIF	Variance Inflation Factor
WA	Western Australia
WHO	World Health Organization
WTP	Willingness to pay
YLD	Years Lost due to Disability
YLL	Years Life Lost

List of published and under review articles included in the thesis

Article I:

Rashidul Alam Mahumud*, Khorshed Alam, Jeff Dunn, Jeff Gow. Emerging cancer incidence, mortality, hospitalisation, and associated burden among Australian cancer patients, 1982-2014: An incidence-based approach in terms of trends, determinants and inequality. *BMJ Open* 2019; 9(12): e031874. (Quartile-1 ranked; Impact Factor: 2.376; SJR = 1.321; SNIP = 1.145; Publisher: BMJ Publishing Group).

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Article II:

Rashidul Alam Mahumud*, Khorshed Alam, Jeff Dunn, Jeff Gow. The impact of lifestyle risk factors, life satisfaction and chronic exposure on changing in longitudinal health status burden among Australian cancer patients, 2013-2017. *BMJ Open* (under review). (Quartile-1 ranked; Impact Factor: 2.376; H-Index: 69; SJR = 1.321; SNIP = 1.145; Publisher: BMJ Publishing Group).

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Article III:

Rashidul Alam Mahumud*, Khorshed Alam, Jeff Dunn, Jeff Gow. The burden of chronic diseases among Australian cancer patients: Evidence from a longitudinal exploration, 2003-2017. *PLoS ONE* 15(2): e0228744 (Quartile-1 ranked, Impact Factor: 2.392; H-Index: 268; SJR = 1.100; SNIP = 1.123; Publisher: Public Library of Science).

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Article IV:

Rashidul Alam Mahumud*, Khorshed Alam, Jeff Dunn, Jeff Gow. The changing relationship between health burden and work disability of Australian cancer survivors, 2003-2017: Evidence from a longitudinal survey. *BMC Public Health* 2020; 20 (548):1-14 (Quartile-1 ranked, Impact Factor: 2.567; H-Index: 117; SJR = 1.382; SNIP = 1.342; Publisher: Springer Nature).

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Article V:

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Article VI:

Rashidul Alam Mahumud*, Khorshed Alam, Jeff Dunn, Jeff Gow. The cost-effectiveness of controlling cervical cancer using a new 9-valent human papillomavirus vaccine among school-aged girls in Australia. *PLoS ONE* 2019; 14(10): e0223658. (Quartile-1 ranked, Impact Factor: 2.392; H-Index: 268; SJR = 1.100; SNIP = 1.123; Publisher: Public Library of Science).
DOI: https://doi.org/10.1371/journal.pone.0223658.

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Article -I:

Rashidul Alam Mahumud*, Jeff Gow, Khorshed Alam, Syed Afroz Keramat, Md Golam Hossain, Marufa Sultana, Abdur Razzaque Sarker, Sheikh M. Shariful Islam. Cost-effectiveness of the introduction of two-dose bi-valent (Cervarix) and quadrivalent (Gardasil) HPV vaccination for adolescent girls in Bangladesh. *Vaccine* 2019; 38(2): 165-172 (Quartile-1 ranked, Impact Factor: 3.269; H-Index: 164; SJR = 1.759; SNIP = 1.128; Publisher: Elsevier).
DOI: https://doi.org/10.1016/j.vaccine.2019.10.037.

Article -II:

Rashidul Alam Mahumud*, Nausad Ali, Nurnabi Sheikh, Raisul Akram, Khorshed Alam, Jeff Gow, Abdur Razzaque Sarker, Marufa Sultana. Measuring perinatal and postpartum quality of life of women and associated factors in semi-urban Bangladesh. *Quality of Life Research* 2019; 28 (11): 2989-3004 (Quartile-1 ranked, Impact Factor: 2.392; H-Index: 128; SJR = 1.142; SNIP = 1.269; Publisher: Springer Nature).
DOI: https://doi.org/10.1007/s11136-019-02247-0.

Article -III:

Rashidul Alam Mahumud*, Khorshed Alam, Andre M. N. Renzaho, Abdur Razzaque Sarker, Marufa Sultana, Nurnabi Sheikh, Lal B. Rawal, Jeff Gow. Changes in inequality of childhood morbidity in Bangladesh 1993-2014: A decomposition analysis. *PLoS ONE 2019*; 14(6): e0218515 (Quartile-1 ranked, Impact Factor: 2.392; H-Index: 268; SJR = 1.100; SNIP = 1.123; Publisher: Public Library of Science).
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Article -IV:

Rashidul Alam Mahumud*, Nadia Ishrat Alamgir, Md Tarek Hossain, Elaine Baruwa, Marufa Sultana, Jeff Gow, Khorshed Alam, Syed Masud Ahmed, Jahangir A M Khan. Women's preferences for maternal healthcare services in Bangladesh: Evidence from a discrete choice experiment. *Journal of Clinical Medicine* 2019; 23;8(2):1-21 (Quartile-1 ranked, Impact Factor: 5.688; H-

Index: 16; SJR = 2.27; SNIP = 1.789; Publisher: Multidisciplinary Digital Publishing Institute, MDPI).
DOI: https://www.ncbi.nlm.nih.gov/pubmed/30678044.

Article -V:

Khorshed Alam, **Rashidul Alam Mahumud**, Fariha Alam, Syed Afroz Keramat, Michael O Erdiaw-Kwasie, Abdur Razzaque Sarker. Determinants of access to eHealth services in regional Australia. *International Journal of Medical Informatics* 2019; 131:1039 (Quartile-1 ranked; Impact Factor: 2.731; H-Index: 93; SJR=0.96; SNIP = 1.633; Publisher: SAGE).
DOI: https://doi.org/10.1016/j.ijmedinf.2019.103960

Article -VI:

Rashidul Alam Mahumud*, Syed Afroz Keramat, Gail Ormsby, Marufa Sultana, Lal B Rawal, Khorshed Alam, Jeff Gow, Andre M. N. Renzaho. Wealth-related inequalities of women's knowledge of cervical cancer screening and service utilisation in 18 resource-constrained countries: Evidence from a pooled decomposition analysis. *International Journal for Equity in Health* 2020; 19 (42):1-15 (Quartile-1 ranked, Impact Factor: 2.988; H-Index: 46; SJR = 1.256; SNIP = 1.167; Publisher: Springer Nature).
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Article -VII:

Rashidul Alam Mahumud*, Jeff Gow, Syed Afroz Keramat, Sonja March, Jeff Dunn, Khorshed Alam, Andre M. N. Renzaho. Distribution and predictors associated with the use of breast cancer screening services among by women aged 40 years or more in 14 low-resource countries. *BMC Public Health* (under review-3rd revision submitted) (Quartile-1 ranked, Impact Factor: 2.567; H-Index: 117; SJR = 1.382; SNIP = 1.342; Publisher: Springer Nature).
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Article -VIII:

Rashidul Alam Mahumud*, Jeff Gow, Abdur Razzaque Sarker, Marufa Sultana, Md. Golam Hossain, Khorshed Alam. Distribution of wealth-stratified inequalities on maternal and child health parameters and influences of maternal related factors on improvements in the child health survival rate in Bangladesh.

Journal of Child Health Care 2020*:*1-17 (Quartile-1 ranked, Impact Factor: 1.505; H-Index: 30; SJR = 0.51; SNIP = 0.911; Publisher: SAGE).
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Article -IX:

Rashidul Alam Mahumud*, Khorshed Alam, Syed Afroz Keramat, Andre M. N. Renzaho, Md. Golam Hossain, Rezwanul Haque, Gail M Ormsby, Jeff Dunn, Jeff Gow. Wealth stratified inequalities in service utilisation of breast cancer screening across the geographical regions: A pooled decomposition analysis. Archives of Public Health 2020 (In-press) (Quartile-1 ranked; H-Index: 21; SJR = 0.853; SNIP = 1.197; Publisher: Springer Nature).
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Article -X:

Sayem Ahmed, Abdur Razzaque Sarker, Marufa Sultana, **Rashidul Alam Mahumud**, Felix Roth, Md Kamruzzaman, Md Zahid Hasan, Andrew J. Mirelman, Ziaul Islam, Louis Wilhelmus Niessen, Clas Rehnberg, AK Azad Khan, Niklaus Gryr, Jahangir A.M. Khan. Do Employer-Sponsored Health Insurance Schemes affect the Utilization of Medically Trained Providers and Out-of-pocket Payments among Ready-Made Garment Workers? - a Case-Control Study in Bangladesh. *BMJ Open* 2020; 0:e030298. (Quartile-1 ranked; Impact Factor: 2.376; SJR = 1.321; SNIP = 1.145; Publisher: BMJ Publishing Group).
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Article XI:

Abdur Razzaque Sarker, Ziaul Islam, Marufa Sultana, Nurnabi Sheikh, **Rashidul Alam Mahumud**, Md Taufiqul Islam, Robert Van Der Meer, Alec Morton, Ashraful Islam Khan, John David Clemens, Firdausi Qadri, Jahangir A M Khan. Willingness to Pay for Oral Cholera Vaccines in Urban Bangladesh. PLoS ONE 15(4): e0232600. (Quartile-1 ranked, Impact Factor: 2.392; H-Index: 268; SJR = 1.100; SNIP = 1.123; Publisher: Public Library of Science).
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Chapter-1: Introduction

Chapter 1: Introduction

1.1 Introduction

The overarching aim of this thesis is to investigate the burden of cancer on patients, households, as well as on society over time. This thesis also aims to generate evidence for health policymakers, who make nationwide cancer control and management decisions, though, for example, the introduction of early cancer prevention programs (e.g., cancer vaccination). This thesis has examined the burden of cancer using a geographical lens, including regional, rural, and remote Australia. The thesis has also further examined the impact of the cancer burden in terms of long-term cancer outcomes, health status burden, chronic comorbid conditions, work-related disability and the economics of cancer vaccination. A quantitative approach is adopted in this thesis. This is a thesis by publication. In this introduction section, the cancer background context is explained as a public emergency, and the ongoing debate about cancer research is discussed, as well as the rationale of this thesis in the Australian context explained. It concludes with a conceptual framework which underpins this thesis.

1.2 Background and rationale

Noncommunicable diseases (*NCDs*) are accountable for the majority of global deaths (World Health Organization, 2019). Cancer is expected to rank as the most significant global public health problem and a leading cause of death and illness in the world, including Australia, in the 21st century (Bray, Ferlay, & Soerjomataram, 2018; Fitzmaurice et al., 2018; GBD 2015 Mortality and Causes of Death Collaborators, 2016; Niessen et al., 2018; Yabroff et al., 2011; AIHW, 2019c). In 2019, it was estimated that almost 145,000 new cases of cancer would be diagnosed in Australia, and that 35% of these individuals will eventually die from the disease (AIHW, 2019a). Cancer accounts for the highest burden of disease of any illness, at approximately 18%, followed by cardiovascular disease (14%), musculoskeletal disorders (13%) and mental health (12%) (AIHW, 2019b).

Despite tremendous progress made over the last couple of decades in terms of cancer survival and mortality rates, the cancer incidence rate has increased by 58% between 1982 and 2019 (AIHW, 2019a). The burden of cancers (e.g., lung, bowel, prostate and pancreatic) increases significantly with remoteness from treatment sources and for those individuals living in depressed socio-economic circumstances (Valery *et al.*, 2006; Coory *et al.*, 2013; Teng *et al.*, 2017).

In Australia, approximately 40% of cancer patients are of working age (AIHW, 2019a). Among those in employment, 46% are unable to return to work after an episode of cancer (Bates *et al.*, 2018), and 67% on their return to employment or change their job (Paul *et al.*, 2016). The majority of cancer survivors depend on family, relatives and friends for physical and economic support during their treatment and/or in the last stages of the disease (Doran *et al.*, 2015; Paul *et al.*, 2016; Bates *et al.*, 2018; CanTeen Australia, 2018).

The costs of advanced cancer treatment are a growing concern globally (Luengo-Fernandez et al., 2013), including in Australia (Sullivan *et al.*, 2011; OECD, 2013; Karikios *et al.*, 2014; Vogler *et al.*, 2016). Spending on cancer constitutes approximately 5% of health-care costs in Organisation for Economic Co-operation and Development (*OECD*) countries, and this number is increasing (OECD, 2013). This surge is attributable to increasing incidence and prolonged survival, but also to the high costs of new drugs and technologies (Sullivan *et al.*, 2011; Kelly and Smith, 2014). In Australia, public pharmaceutical expenditure on cancer drugs increased significantly from A$65 million in 1999–2000 to A$466 million in 2011–2012, with an average increase of 19% per year (Karikios *et al.*, 2014). Access to cancer medicine remains a major public health challenge, even in high-income countries such as Australia (Vogler *et al.*, 2016). The increasing costs associated with cancer treatment are not driven exclusively by higher demand for services (Sullivan *et al.*, 2011). This nevertheless creates major challenges for healthcare systems, particularly those like Australia's that are publically funded. However, the ability to deliver affordable cancer care is problematic due to a volatile mixture of demographics (ageing and expanding

populations), rapid development of new technologies (such as medicines and surgery), and increasing health care expenditure which is driving cancer-care costs upwards (Karikios *et al.*, 2014; Kelly and Smith, 2014; Vogler *et al.*, 2016).

As the overall cancer burden increases, the economic loss due to premature cancer-related illness and associated mortality poses the main challenges to poverty alleviation efforts. Furthermore, cancer-related illness results in a number of patients and their households experiencing economic hardship due to high out-of-pocket expenses, lost productivity, loss/reduction of household income, and other induced expenditure (Doran *et al.*, 2015; Paul *et al.*, 2016; Bates *et al.*, 2018; Gordon *et al.*, 2018). Catastrophic healthcare expenditure has been found to occur in more than 60% of diagnosed cancer patient's households (Jan *et al.*, 2018).

The economic burden of cancer is of growing concern for policymakers, healthcare practitioners, physicians, employers, and society overall (Doran *et al.*, 2015; Paul *et al.*, 2016). Considerable progress has been made in recent decades in terms of cancer survival and reduced mortality rates (Tiwari and Roy, 2012; Allemani *et al.*, 2018) through the introduction of primary preventive strategies (e.g., vaccination) and effective collaboration with non-government organisations and other potential stakeholders, including community groups. Therefore, a reduction of cancer incidence, along with improvements in cancer treatments and survival rates, is essential to reduce the burden of the disease.

The increased burden of cancer-related illnesses, together with advanced treatment procedures (including technological innovation) and intensified patient, community, and provider expectations, impose challenges to the affordability as well as affability of health care services for households and governments alike. As a chronic condition, cancer-related illnesses can lead to a devastating, long-term health and economic burden for individuals and their households, particularly in resource-constrained settings. Many patients with cancer-related illness are confronted with the choice of either opting for

treatment, thereby reducing resources available for their families possibly leading to poverty, or declining treatment, which also has adverse health and economic consequences for the individual and their household. For example, 21% of the Australian population with diagnosed cancer have 'skipped' health care services due to the high health care costs (Callander *et al.*, 2017).

Health systems that protect individuals and their households from the economic circumstance of *NCDs*, including cancer, are pivotal if the United Nation's Sustainable Development Goals (*SDGs*) of ineqalities reduction is to be achieved. However, health and economic outcomes are associated with social disadvantage, increases an individual's risk of chronic disease, and pre-disposes them and their households to illness-related poverty and economic hardship through loss of employment and high out-of-pocket costs (Callander *et al.*, 2017, 2019; Jan *et al.*, 2018). This association between *NCDs* and poverty is identified in the *SDGs*, and some of the goals relate directly to measures that reduce the burden of *NCDs* (e.g., reducing premature deaths from *NCDs* by 30%), and strengthening access to essential medicines and universal health coverage. In Australia, the number of cancer patients (due to the demographic transition such as an ageing population) will increase, and course of treatment protocols will be more complex, and therefore more expensive. The challenge of the health system is how to collectively deliver reasonably priced cancer health care services to all exposed citizens i.e., make cancer care affordable for individuals and society alike. This is needed to inform and guide this essential public debate amongst leading members of the cancer community, from patient advocates to economists and health-care professionals.

1.3 The ongoing debate on cancer research

The ongoing debate about cancer research in Australia has been extended to include issues such as over-diagnosis, accessibility, prevention, and societal benefits, with a particular focus on the burden of the cancer disease for patients, households and society. Over-diagnosis is an extremely vexing issue. It can lead to over-treatment of cancer patients (Bleyer and Welch,

2012) and confers short- and long-term risks (Bach, 2008). Consequently, cancer patients often experience other chronic comorbid conditions (Bach, 2008; Braithwaite *et al.*, 2016) and it imposes a higher physiological burden of disease (Stairmand *et al.*, 2015). The presence of specific severe comorbidities or psychiatric disorders is associated with delayed cancer diagnosis (Sogaard *et al.*, 2013). Furthermore, patients with chronic diseases, who have regular medical consultations and follow-up, have their cancer detected at an earlier stage. Thus, any amount of over-diagnosis increases the overall treatment costs (Carter and Barratt, 2017).

Similarly, equitable access to health services (e.g., access to new cancer medicine) is also highly contentious in the context of Australia (Vitry *et al.*, 2016). Moreover, there is an equity concern across regional Australia because cancer patients they have less opportunity to receive health care services than patients in urban areas (Deloitte Access Economics, 2013; Vitry *et al.*, 2016). In the perception of most stakeholders, the ongoing debates about cancer research are challenging and inevitably emotive from the perspective of patients, family, and society (Deloitte Access Economics, 2013). In addition, this debate draws attention as to how Australian society should value the advantages of cancer prevention and control innovations, and how to best facilitate equitable patient access to health care through fair and transparent resource allocation mechanisms, which is a priority concern of cancer research in Australia.

1.4 Emerging risk of cancer

The World Health Organization (*WHO*) has reported that approximately 30-50% of all cancer cases are preventable (WHO, 2019a). There is also a number of avoidable risk factors which contribute to an increasing incidence of cancer. In addition, prevention and early detection of cancer, supported by national policies and programs, are the most cost-effective long-term strategies for the control of cancer. These should be implemented to increase public awareness, to reduce exposure to cancer risks and to ensure that people are provided with the relevant information and support they need to adopt healthier lifestyles.

(a) Tobacco use

The harmful use of tobacco is one of the leading avoidable risk factors for cancer incidence and cancer-related mortality. Worldwide, approximately 6 million people die each year from cancer and other *NCDs* (WHO, 2019a). Tobacco smoking contributes to the development of several types of cancer (e.g., cancers of the lungs, larynx, mouth, throat, kidneys, bladder, pancreas, stomach, cervix, and oesophagus). A recent study conducted in Australia found that approximately 13% of all cancers were attributable to exposure to tobacco smoking, including 81% in lungs, 60% in oesophagus, 59% in oral cavity and pharynx, and 6% in colorectal cancers (Pandeya *et al.*, 2015). Cancer Australia reported that more than one in eight cancers are attributed to tobacco smoking, and could be avoided if nobody smoked (Cancer Australia, 2014a). Strategies to reduce the prevalence of smoking remain a high priority for cancer control authorities (WHO, 2013; Cancer Australia, 2014a).

(b) Alcohol use

The harmful use of alcohol is a serious health burden. Health problems from excessive alcohol use arise in the form of acute and chronic conditions, and adverse social consequences are common. Alcohol consumption is a dominating risk factor for developing many cancer types (e.g., cancer of the liver, colorectal, oral cavity, pharynx, larynx, oesophagus, and breast) (Meyer *et al.*, 2019; Wilson *et al.*, 2019). The risk of cancer increases with the amount of alcohol consumed (Chu *et al.*, 1990; Grevers *et al.*, 2019; Meyer *et al.*, 2019; Wilson *et al.*, 2019). For several types of cancer, heavy drinking of alcohol, combined with the use of tobacco, predominantly increases the high risk of cancer (Chu *et al.*, 1990; Grevers *et al.*, 2019; Meyer *et al.*, 2019; Wilson *et al.*, 2019). To combat alcohol abuse, most global strategies focus on key areas of policy regulation and enforcement (WHO, 2013, 2018a, 2019a; Cancer Australia, 2014a). Through public health advocacy and partnerships, national interventions focus on resource mobilisation, the provision of

technical support and capacity building, and knowledge dissemination (WHO, 2013, 2018a, 2019a; Cancer Australia, 2014a).

(c) Physical inactivity, dietary factors, and obesity

Dietary modification is another significant mode of controlling cancer-related illness. There is a significant association between obesity and many types of cancer (e.g., oesophagus, colorectal, breast, endometrium and kidney cancer). For example, diets high in meat and reduced fibre are associated with colon cancer. Fruits and vegetables may have an independent protective effect against many cancers (Ambrosini *et al.*, 2008; Lee *et al.*, 2017; Afshin *et al.*, 2019; WHO, 2019b). Furthermore, an adequate level of physical activity and the maintenance of a healthy body weight, along with a healthy and balanced diet, reduces cancer risk significantly (Loprinzi *et al.*, 2012; Afshin *et al.*, 2019; Lacombe *et al.*, 2019). Therefore, healthy eating practices that prevent the development of diet-related cancers will also lower the risk of other *NCDs*. Improved prevention strategies are needed to encourage individuals to implement improved lifestyle habits.

(d) Infections

A number of human oncogenic infectious agents, for instance human papillomavirus (*HPV*), helicobacter pylori, hepatitis B and C, and the Epstein-Barr virus, are significantly attributed in 15% of all cancers worldwide (WHO, 2019a). Persistent infections with HPV are a key cause of cervical cancer and it is an established carcinogen of cervical cancer (Forman *et al.*, 2012). HPV is predominantly transmitted to reproductive-aged women through sexual contact (CDC, 2015). Most *HPV* infections are transient, and individuals are cured within a short duration of time, usually within a few months after their acquisition. However, *HPV* infections can continue and evolve into cancer without treatment. There are more than 100 types of *HPV* infections that have been identified so far and they can be divided into low- and high-risk types in terms of developing into cervical cancer (Mennini *et al.*, 2017). Thirteen high-risk *HPV* types are known to be predominantly responsible

for malignant and premalignant lesions of the anogenital area (Guan *et al.*, 2012), and they are the leading cause of the most aggressive cervical cancers (Li *et al.*, 2011). Furthermore, *HPV* is also responsible for the majority of anogenital cervical cancers, such as anal cancers (88%), vulvar cancers (43%), invasive vaginal carcinomas (70%), and all penile cancers (50%) (Mennini *et al.*, 2017). Cervical cancer is preventable through implementation of a primary prevention strategy such as vaccination (Jit *et al.*, 2014; Patel *et al.*, 2018).

Helicobacter pylori (*HP*) is a gastric pathogen that colonises approximately 50% of the world's population (Wroblewski *et al.*, 2010). Infection with *HP* causes chronic inflammation and significantly increases the risk of developing duodenal and gastric ulcer disease and gastric cancer. Infection with *HP* is the strongest known risk factor for gastric cancer, which is the second leading cause of cancer-related deaths worldwide. Once *HP* colonizes the gastric environment, it persists for a lifetime in the host, suggesting that the host immune response is ineffective in clearing this bacterium (Wroblewski *et al.*, 2010).

The viral hepatitis pandemic takes a heavy toll on lives, communities and health systems (Orlando *et al.*, 2015). Cancer caused by infection with the Hepatitis B virus (*HBV*) is a major global health problem (WHO, 2019c). It is estimated that approximately 257 million people are infected with *HBV*, which is defined as hepatitis B surface antigen-positive–HBVsAgþ (WHO, 2019c). As a consequence, *HBV* resulted in 887,000 deaths, predominantly from cirrhosis and hepatocellular cancer, in 2015 (WHO, 2019c). The virus is highly infectious and abundantly found in blood and body fluids of infected persons, many of whom are asymptomatic and unaware of their disease (Orlando *et al.*, 2015). Furthermore, *HBV* is transmitted via the parenteral route, infusion of infected blood or blood products, needle sharing, penetration of micro-wounds on skin or mucosae. (Orlando *et al.*, 2015; WHO, 2016a, 2019c).

Since 1982, *HBV* infection has been preventable by vaccination. The *HBV* vaccine is one of the most effective vaccines of neonates and infants, resulting in decreased rates of new infections and chronic liver disease, including cancer and hepatocellular carcinoma (Mikaeloff *et al.*, 2001). Currently, 130 countries, including Australia, implement the hepatitis B vaccine in their routine vaccination schedules for infants and/or adolescents (Goldstein and Fiore, 2001). In Australia, vaccination against hepatitis B was introduced in the early 1980s and targeted those at most risk of infection (AIHW, 2018a). Free infant vaccination was implemented in 1990 in the Northern Territory and was eventually rolled out nationally in 2000 (AIHW, 2018a). The Australian National Immunisation Program now provides vaccination against hepatitis B at birth and during infancy. Vaccination is also recommended for some adults who are at higher risk, for instance, people who have had organ transplant, people with certain liver or kidney problems, and people who travel to countries where hepatitis B is common. In 2017, 95% of Australian one-year-olds were fully vaccinated against hepatitis B (AIHW, 2018a; Ioannides *et al.*, 2019). The current strategies for controlling *HBV* infection include active immunization, passive immunization and chemoprophylaxis with antiviral drugs (Orlando *et al.*, 2015; WHO, 2016a). Passive immunization and chemoprophylaxis can also contribute to the control of *HBV* infection.

1.5 Australian health care system

As a national goal, the Australian's health system (*AHS*) provides quality and affordable health care services for all Australians. All three levels of government are involved: federal (financing), state and territory (funding and service delivery), and local (service delivery) (Australian Government, 2019a). The foundation of *AHS* is the publically funded national universal health insurance scheme, *Medicare*, and its predecessor Medibank, which commenced in the 1970s to promote universal health care by providing safe and affordable health care services for Australians. Through *Medicare*, patients are able to access free or subsidised medical services, treatment in

public hospitals free of charge, and receive subsidises with respect to some procedures provided in private hospitals. Through the pharmaceutical benefits scheme, patients are also able to receive a subsidy for medicines. Those eligible to access health care services through Medicare include Australian and New Zealand citizens, permanent residents of Australia, and individuals who have applied for a permanent visa (Department of Health, 2019). Patients are provided with a rebate benefit for health care services for out of hospital services. However, overseas student health cover (*OSHC*) is mandatory for all international students, to ensure that they and their dependents can access affordable healthcare whilst living and studying in Australia.

The rebate amount is case-dependent. For example, for a consultation with a General Practitioner, specialist or consultant physician, with a duration of at least 10 minutes for a cancer patient to develop a multidisciplinary treatment plan, the scheduled payment was $81.50 in 2019, and the benefit was 100% of the scheduled fee; hyperbaric oxygen therapy associated with treatment of localised non-neurological soft tissue radiation injuries had a scheduled fee of $254.75 and the benefit was 75% of the schedule fee, or $191.10 (Department of Health, 2019). While public hospitals are free of charge, the majority of out of hospital health care services are provided by private health providers. The actual amount of fees for service is set by the providers themselves and are not regulated, meaning that private healthcare providers can have fees above the scheduled payment. Any difference between the amount of the provider's fee for a service and the amount of rebate is paid by the patient from their out-of-pocket (*OOP*) expenses. For example, if the actual amount charged by the provider is $81.50 for a diagnostic (e.g., blood) test, Medicare would provide a rebate of $61.10 (75% of the schedule fee), leaving the patient to pay $20.40. *Medicare* has additional policies to protect patients from catastrophic *OOP* healthcare payments. In this context, health care cards are provided to welfare recipients and low-income earners, and other eligible patients who pay a lower *OOP* payment for prescription medicines (Department of Human Services, 2019a).

The '*Medicare Safety Net*' and '*Extended Medicare Safety Net*' programs also provide higher rebates if an individual or family group reaches a certain level of total expenditure on *OOP* fees within a calendar year. Any subsequent services or prescriptions will have a higher proportion of subsidy for the rest of that calendar year (Duckett and Willcox, 2015). Under the '*Medicare Safety Net'*, once the threshold has been reached then 100% of the schedule fee for all health care services is rebated; and under the '*Extended Medicare Safety Net*' 80% of the actual *OOP* payments is rebated (Department of Human Services, 2019b).

1.6 Existing studies

1.6.1 Unequal distribution and emerging burden of cancer outcomes

Cancer is a life-threatening disease that leads to a huge health and economic burden during the treatment and oncology follow-up periods. However, certain groups (e.g., those affected by disability, remoteness, and disadvantaged socioeconomic status) of the population are more prevalent in bearing a disproportionate burden of cancer outcomes (e.g., incidence, mortality, hospitalisation) compared with other more advantaged groups (Heathcote and Armstrong, 2007; Elwood *et al.*, 2016; Bergin *et al.*, 2018; Goodwin *et al.*, 2018; Arnold *et al.*, 2019; Khan; *et al.*, 2019). The magnitude of comorbid conditions (during course of treatment and follow-up periods) among cancer patients in Australia is also more pronounced for people aged 65 years and over (87%) compared with people aged 0-44 (35%); people from a deprived socioeconomic background (55%) compared with their more advantaged counterparts (47%); and people living in regional and remote areas (54%) compared with those in the major cities (48%) (AIHW, 2016a).

In Australia, economic disparities between socio-economically advantaged and disadvantaged individuals and groups are increasing as a result of the growing burden of cancer (Coory *et al.*, 2013). There are several reasons that might contribute to this disparity, directly or indirectly. The paucity of appropriate health care services is significantly worse in resource-constrained

settings, including geographically underprivileged locations compared to privileged people and communities with easier access to a greater range of cancer services, improved knowledge and awareness of cancer prevention strategies, and better and more easily accessible health facilities and resources (Blinman *et al.*, 2012; Coory *et al.*, 2013; Cancer Australia, 2014). Other common reasons for such disparities include limited affordability and accessibility of cancer care services for population of socio-economically underprivileged groups (Valery *et al.*, 2006), and their inadequate utilisation of healthcare services (Bernardes *et al.*, 2012). This imbalance contributes to an increasing burden of cancer outcomes and leads to a greater burden for the individual, family and society, which is exacerbated for the more underprivileged.

In the recent past, disparities related to cancer outcomes have become the subject of an international focus and new service initiatives (Yabroff *et al.*, 2011; Fitzmaurice *et al.*, 2018). In 2016, the *WHO* Executive Board recommendation was to strengthen health systems to ensure early detection and diagnosis, as well as enable accessible, affordable, and appropriate and quality healthcare services for all patients with cancer (WHO, 2016b). Only a few studies have focused explicitly on socio-economic inequality of cancer care and healthcare utilisation in Australia. In recent decades, the incidence of cancer has increased (Baade *et al.*, 2010; Adama *et al.*, 2018; Allemani *et al.*, 2018; Bray *et al.*, 2018; Luo *et al.*, 2019), which has been more pronounced among adolescents and young adults (Roder *et al.*, 2018), and older adults (Feletto *et al.*, 2019), yet cancer-related mortality rates have slightly dropped (Carioli *et al.*, 2018). In Australia, some types of cancer have the highest rates in the world: melanoma (Roder *et al.*, 2018), keratinocyte, and melanocyte (Lai *et al.*, 2018). Australia and New Zealand together have the highest rates for merkel cell carcinoma (Stang *et al.*, 2018; Lee *et al.*, 2019). Some of these studies have focused on geographical or socioeconomic disparities in cancer care and survival (Fox and Boyce, 2014; Baade *et al.*, 2016; Stanbury *et al.*, 2016; Tervonen *et al.*, 2016a, 2016b, 2017b, 2017a).

1.6.2 Long-term health status burden of cancer patients

Studying health status among cancer survivors is warranted, and has attracted considerable attention in the public health domain. Even with advanced treatment of side effects, cancer survivors undergo experiences that often reduce their capacity to conduct their usual activities, which in turn may affect their overall health status. In recent decades, measuring health status has been integrated into the examination of treatment impacts on quality of life (Tan *et al.*, 2019). Health status assessments have become routine and are used to evaluate health status in terms of treatment outcomes (Arraras *et al.*, 2018; Su *et al.*, 2019; Tan *et al.*, 2019). Despite this, very little attention has been paid to measuring the longitudinal health status burden of diagnosed cancer survivors during the oncology follow-up period.

Some studies have focused on the impact of treatment or surgical outcomes in relation to health status, and access to palliative care in different national settings (Elliott *et al.*, 2004; Dunn *et al.*, 2013; Thomas *et al.*, 2014; Garvey *et al.*, 2016; Haugland *et al.*, 2016; Arraras *et al.*, 2018). The health status of cancer survivors can be adversely affected by side effects (Shin *et al.*, 2017), such as compromised nutritional status (Capuano *et al.*, 2010), and eating problems (Spielman, 1998). Moreover, engaging in physical activities can lead to improved health status outcomes among cancer survivors (Shin *et al.*, 2017). Similarly, cancer survivors who engage in less sedentary behaviour enjoy a better quality of life, and this can also significantly contribute to reducing the risk of chronic comorbid conditions (AIHW, 2017). Furthermore, the comorbid condition of cancer survivors is an important parameter to predict poor health status (Der-Martirosian *et al.*, 2013; Banham *et al.*, 2018).

1.6.3 Long-term chronic comorbid conditions of cancer patients

Most cancer patients suffer from multiple chronic diseases or conditions, commonly referred to as comorbidity. Comorbidity has a well-documented detrimental effect on cancer survival (Sarfati *et al.*, 2016a) and it describes

the existence of a long-term health condition or disorder in the presence of a primary disease or illness (Sarfati *et al.*, 2016b). A number of studies have confirmed that comorbid chronic conditions were more pronounced among cancer patients (Gross *et al.*, 2007; Sarfati *et al.*, 2009; Sogaard *et al.*, 2013; Lindhagen *et al.*, 2015; Siegel and Wisnivesky, 2017; Cuthbert *et al.*, 2018; Ng *et al.*, 2018). The most prevalent risk factors are amongst older population groups (aged 65 years or more) (Yancik *et al.*, 2001; Yun *et al.*, 2007), tose with unhealthy behaviours (e.g., alcohol consumption and smoking tobacco) (Grimmett *et al.*, 2009; Ezzati and Riboli, 2013), obesity (Loprinzi and Cardinal, 2012) and inadequate diet (Ezzati and Riboli, 2013). These factors are significantly associated with a higher risk of developing cancer along with chronic comorbid conditions (Ezzati and Riboli, 2013; Stairmand *et al.*, 2015; AIHW, 2018b). The ongoing evidence shows that modifying or avoiding risk factors can significantly reduce the burden of chronic comorbid conditions among cancer patients (WHO, 2018b).

The risk of having comorbidity increases during treatment as well as oncology follow-up periods (AIHW, 2018b, 2019c; WHO, 2018c), which can adversely influence treatment choices and health outcomes. Chronic comorbid conditions of cancer patients contribute to major clinical challenges, including diagnosis, ill health, treatment, long-term health conditions and disease management (Stairmand *et al.*, 2015). In 2014-15, more than 11 million Australians (50%) reported having at least one chronic disease, while approximately 1 in 4 (23%) Australians had two or more chronic conditions (AIHW, 2016a). The severity of comorbidity contributes significantly to an increased risk of hospitalisation, reduced health status, increased risk of mortality, and increased financial burden on the healthcare system (Carstensen *et al.*, 2012; Sogaard *et al.*, 2013; Sarfati *et al.*, 2016a). The chance of improving health status and completing cancer treatment protocol in the presence of comorbid conditions is considerably lower among cancer patients (Elliott *et al.*, 2004; Sarfati *et al.*, 2009; Gurney *et al.*, 2015; Cuthbert *et al.*, 2018; Ng *et al.*, 2018). There is a significant association with a higher rate of mortality depending on the severity of the disease and associated comorbidity (Sogaard *et al.*, 2013). For instance, the mortality rate

is substantially higher among cancer patients with comorbidities (47%) compared with cancer patients without comorbidities (34%) (Van Hemelrijck *et al.*, 2016).

1.6.4 Impact on long-term productivity of cancer patients

Internationally, some studies have focused on cancer survivors' characteristics and work participation, including those in the United States of America (*USA*) (Feuerstein and Harrington, 2006; Short *et al.*, 2008; Oberst *et al.*, 2010; Mehnert, 2011; Mehnert *et al.*, 2013; Tangka *et al.*, 2013; Chrischilles *et al.*, 2019), Canada (Lauzier *et al.*, 2008; Jones *et al.*, 2016), South Korea (Park *et al.*, 2009), the Netherlands (Muijen *et al.*, 2013a, 2013b, 2014), and Belgium (Sullivan *et al.*, 2004; Kiasuwa Mbengi *et al.*, 2018).

Several factors adversely influencing work participation of patients with cancer have been determined in different settings, such as poor economic position (Muijen *et al.*, 2013a, 2013b, 2014; Chrischilles *et al.*, 2019), disease-related factors (e.g., tumour site, advanced tumour stage), side effects of advanced treatment (e.g., chemotherapy) (Muijen *et al.*, 2013a; Yokota *et al.*, 2015; Jones *et al.*, 2016; Chrischilles *et al.*, 2019), and work-related factors (e.g., physical work demands) (Mehnert, 2011; Muijen *et al.*, 2013b). The severity of diseases and the presence of comorbid conditions in cancer patients create a higher likelihood of work-related disability (Jones *et al.*, 2016). A previous study conducted in the Netherlands found that cancer survivors who had experienced hormone therapy to treat metastatic disease, had limited physical strength, and limited workability was strongly and adversely associated with a higher risk of work disability (Muijen *et al.*, 2013a, 2014). The poor perceptions of cancer survivors, in terms of their health and workability (Muijen *et al.*, 2013a), their unhealthy behaviours (e.g., alcohol consumption), and their clinical-stage (Vartanian *et al.*, 2006) were also significant predictors in determining independent effects on their work disability levels. In the context of Australia, some studies among cancer patients have examined the psychological effects of current treatment or level

of disability (Banks *et al.*, 2010), association with work-related stress and chronic illnesses, including cancer (Renzaho *et al.*, 2013), and lost productivity due to cancer (Bates *et al.*, 2018).

1.6.5 Economic of cancer prevention (vaccination) in Australia

Early prevention mechanisms include vaccination, diagnosis, effective screening, adequate referral and advanced course of treatment procedures. In this context, *HPV* vaccinations (i.e., *bivalent and quadrivalent*) have been introduced in many countries in the past decade (Jit *et al.*, 2014). Currently, available *HPV* vaccines can promote herd immunity against cancer-causing types of *HPV,* which helps to reduce the high-risk of the cervical cancer burden. These vaccines have played a significant role in preventing *HPV* infection types 16 and 18 (Jit *et al.*, 2014), which cause more than 70% of cervical cancers in Australia (Li *et al.*, 2011).

In 2007, Australia was the first country to implement a publicly-funded National *HPV* Immunisation Program (*NHIP*), starting with pre-adolescent girls, using the quadrivalent Gardasil® vaccine (*4vHPV*; Merck & Co., Kenilworth, NJ, USA) (Georgousakis *et al.*, 2012). This program for adolescents employed a three-dose schedule of the *4vHPV* vaccine (Australian Government, 2019b). The *4vHPV* vaccine provides protection against *HPV* infection types 6, 11, 16, and 18 (Smith and Canfell, 2017). Later in 2018 in Australia, the *4vHPV* vaccine was replaced by the two-dose nonavalent Gardasil®-9 vaccine (*9vHPV*; Merck Sharp & Dohme) (Office of the Prime Minister of Australia, 2017). According to the underlying distribution of *HPV* infection types of cervical cancers, the *9vHPV* vaccine builds population-level strong immunity against *HPV*-6, 11, 16, 18, 31, 33, 45, 52, and 58 infections (Guan *et al.*, 2012) that cumulatively contribute to approximately 89% of all cervical cancers globally (Serrano *et al.*, 2012) and 93% in Australia (Brotherton *et al.*, 2017). Considering the primary prevention of *HPV* infection, the *9vHPV* vaccine is anticipated to reduce, by 10%, the lifetime risk of a diagnosis of cervical cancer in immunised cohorts

compared to the *4vHPV* vaccine, and by 52% compared to non-vaccinated cohorts (Simms *et al.*, 2016).

With the availability of vaccines for the different *HPV* infection types, there are good opportunities for primary prevention to add to continuing efforts related to secondary prevention strategies. However, the decision for any country to add a new vaccine to national immunisation programs requires careful assessment of the relative value of the vaccine compared with alternative uses of the required resources (i.e., cost-effectiveness) and its affordability (i.e., budgetary impact).

There is considerable evidence that attest to the cost-effectiveness of the *9vHPV* vaccine in different country settings. In Canada, the *9vHPV* was found to be highly cost-effective compared with the *4vHPV* vaccine, taking into consideration the shorter duration of protection (*9vHPV* = 20 years vs. *4vHPV* = lifelong), along with a lower vaccine efficacy (85% vs. 95%) (Drolet *et al.*, 2014). In other studies conducted in the USA, the *9vHPV* vaccine was also found to be very cost-effective compared to the *4vHPV* vaccine (Chesson *et al.*, 2018). However, findings of cost-effective evaluations differ based on study settings, funding, perspectives and coverage of vaccination.

For example, in the *USA*, Chesson et al. (2016) found that the *9vHPV* vaccine was not cost-effective, with an incremental cost-effectiveness ratio (*ICER*) of $146,200 per quality-adjusted life-year (*QALY*) gained, which exceeded the cost-effectiveness threshold ($100,000) (Chesson *et al.*, 2016). Some cost-effectiveness evaluations were performed using the same vaccine (i.e., 9-valent) in the *USA* to capture the different dimensions of its economic viability (Brisson *et al.*, 2016; Chesson *et al.*, 2016; Laprise *et al.*, 2016; Markowitz *et al.*, 2016). These studies incorporated different study participants, designs, perspectives, vaccine delivery routes and model specifications.

A recent study conducted in both Australia and Canada focused on the *9vHPV* vaccine in terms of screening scenarios (Simms *et al.*, 2016) and they found that *9vHPV* had a significant impact on reducing cervical cancer incidence. Furthermore, they claimed that the incremental cost per dose for girls should not exceed a median of A$35.99. However, this study emphasised the impact of vaccines to prevent cervical cancer rather than their economic viability. Significantly, sufficient evidence did not arise for health policymakers to use the findings to develop cost-effective intervention strategies. In Germany, universal immunisation with *9vHPV* was suggested, as it had an *ICER* of €22,987/*QALY* gained, which was below the threshold (Largeron *et al.*, 2017). In Spain, a recent study evaluated a vaccine program in adolescent girls, as part of which the *9vHPV* vaccine was found to be highly cost-effective, with an *ICER* of €7,718 per *QALY* compared to the *4vHPV* vaccine (Fuente *et al.*, 2019). In Kenya and Uganda, a study recommended that the *9vHPV* vaccine was highly cost-effective in both countries, as the additional cost of the *9vHPV* vaccine did not exceed I$8.3 per immunised girl (Kiatpongsan and Kim, 2014).

1.7 Research gap

The themes for this research have been developed based on the academic literature and grey literature and anecdotal evidence as well as ongoing public and policy debates about cancer research. Most studies pay little attention to analysing the long-term health and economic impacts with analytical rigour. Thus, their evidence is not sufficient for health policymakers to develop effective or conclusive strategies in relation to the levels of the burden of cancer. Empirical evidence in the Australian context is also limited, in terms of long-term cancer outcomes, to measure the trends, associated determinants and magnitude of socio-economic inequalities of cancer outcomes (e.g., incidence, mortality, hospitalisation, and burden of cancer) over time. Therefore, national-level trends, differential socio-economic inequality of cancer outcomes, as well as influential factors associated with the cancer burden in Australia are unclear.

The *first study* of this thesis examines the national level cancer outcomes in Australia and considered an incidence-based approach in terms of trends, determinants and inequality over the last three decades (see Figure 1). Furthermore, the main intention of the majority of previous studies (by conducting a cross-sectional, clinical or randomised control trial) was to investigate the impact of treatment or surgical outcomes on health status, while adjusting for a limited range of confounders. Most studies pay little attention to examining the long-term health status burden of cancer survivors over time. Therefore, it is significant for routine oncology follow-ups to explore how cancer survivors' characteristics impact on their health status outcomes over an extended period.

The *second study* of this thesis focuses on quantifying the long-term health status burden and associated risk factors (e.g., lifestyle, life satisfaction, associated chronic diseases) of cancer survivors using a longitudinal approach. The longitudinal effect was captured using generalized linear mixed model (*GLMM*), which estimated changes in health status burden influenced by socio-demographic, lifestyle, life conditions and location-specific variables.

Given the clinical significance of comorbidity and its prevalence in cancer survivors, it is essential to have a measure to quantify the likely effects on cancer outcomes (Pule *et al.*, 2018). However, understanding more about comorbidities among cancer patients can also generate possible evidence as well as provide direction for prevention, management, and treatment of chronic diseases. The primary intention of the existing studies was to examine the distribution, trend, pattern, and disparity in comorbidity status among cancer patients when considering a limited range of variables. The majority of studies pay little attention to examining the long-term impact of chronic comorbid conditions for cancer survivors over time, and which is unclear in Australia. Therefore, routine oncology follow-ups should explore how cancer survivors' characteristics impact on the number of chronic comorbid conditions they experience. The *third study* addresses this gap by

examining the longitudinal nature of chronic comorbid conditions of cancer patients using health economics analytics and a fixed-effect negative binomial regression model and employing a longitudinal design to analyse Household, Income and Labour Dynamics in Australia (*HILDA*) survey data.

Considering the economic burden, few studies have examined the health burden in relation to the work-related disability of cancer survivors. The potential factors associated with work disability of cancer survivors are poorly explored. This may be partially accounted for by the variety in study designs, analytical rigour and follow-up periods. For instance, many international studies have used a limited number of predictors. A number of previous studies have been cross-sectional in nature in terms of their clinical and treatment perspectives. Thus, a study to examine the impact of the health burden in relation to the magnitude of work disability for a long-term sequela of patients with cancer is relevant. There is increased interest in cancer survivorship, leading to efforts to identify and manage treatment-related sequelae, enhance the quality of life, and improve the overall functioning of people who are receiving long-term follow-up care after cancer treatment.

The *fourth study* therefore, aims to investigate the distribution, potential predictors and associated burden of chronic comorbid conditions among cancer patients by using a longitudinal data set for Australia. The longitudinal effect was captured using a fixed effect multinomial logistic regression model, which predicted changes in the relationship between cancer burden and work disability level, while controlling for socio-demographic, lifestyle and life conditions predictors.

Finally, some limitations have been identified in the existing findings of cancer preventative and control programs with regards to their economic viability, due to the hypothetical programs and populations used. Previous cost-effective evaluations have only considered one perspective usually related to the health system or societal, or both perspectives, along a single vaccine delivery route. In Australia, the *9vHPV* vaccine was introduced in 2018. However, there is no current comprehensive evidence concerning the

economic viability of the *9vHPV* vaccine in Australia across delivery strategies (e.g., school-based, health facility-based and outreach-based) from the health system and societal perspectives. In this context, comprehensive evidence with regard to the economic viability of new cancer vaccines is significant for determining the optimal pricing of delivery strategies in the vaccination program in order to maximise the societal benefits of the introduction of the vaccines in Australia.

The *fifth study* evaluates the cost-effectiveness of the *9vHPV* vaccine from both the health system and societal perspectives across three delivery routes. Before conducting this cost-effectiveness evaluation of the *9vHPV* vaccination, a systematic review was conducted to update and investigate general trends as part of an ongoing cost-effectiveness evaluation with regard to the economic viability of *HPV* vaccination within a global context.

1.8 Research aim and research questions

The main aim of this thesis is to measure the burden of cancer and examine the longitudinal impact on cancer survivors, their households, as well as on society generally. This thesis has examined the burden of cancer across geographical distribution, including regional, rural, and remote Australia. The study has also examined the impact in terms of long-term cancer outcomes, health status burden, chronic comorbid conditions, and productivity related work disability. While an economics of cancer vaccination study could potentially have been conducted in this setting, a quantitative approach was adopted based on the research questions, modelling framework, the expertise of the student and the supervisors. To achieve the research goals outlined above, five studies (*Studies 1-5*) were conducted. The following table (Table 1) lists the objectives and research question of each publishable paper written for this thesis.

1.9 Study design and perspective

The present research work has evolved based on the aims of the thesis, and has been focused within the ongoing debates around cancer. All these studies were quantitative in nature, utilising health economic methods and advanced statistical techniques. This thesis is based on five studies using different but established study designs and approaches. All studies had a national and international context, and used published data sources related to cancer. This thesis is constructed based on three main themes including 'understanding of the challenges of cancer outcomes', 'long-term cancer burden (i.e., health status burden, chronic comorbid conditions, productivity-related work disability and its consequences)', and 'evaluation of cancer prevention program' in the context of Australia (Figure 1).

Study 1 used an incidence-based approach restricted to the publicly accessible *AIHW* database, which extended understanding the challenges of cancer diseases in terms of incidence, mortality, hospitalisation and associated burden of diagnosed cancer patients in Australia. *Studies 2-4* used a longitudinal study design, using *HILDA* datasets that examined the long-term impact on health status burden, comorbidities, associated work-disability, and their consequences related to cancer. *Study 2* focused on the impact of health status burden and its consequences on cancer patients (Figure 1).

A longitudinal exploration concerning the burden of cancer on chronic comorbid conditions was examined in *Study 3*, whereas the long-term impact of cancer burden on chronic comorbid conditions and work-related disability were elucidated in *Study 4*. Concerning the burden of cancer, *Study 5* related to the primary prevention of cancer and focused on the economics of cancer vaccination using economic evaluation technique. This study assessed the cost-effectiveness of the new *9vHPV* vaccination used in Australia while considering a broader societal perspective.

As cancer incidence and associated mortality rates still remain a devastating public health concern in Australia, these studies are anticipated to contribute

to generating new knowledge, particularly in the context of the 'economic of cancer vaccination', and could bring added value to ongoing research and exploration in this field (Figure 1).

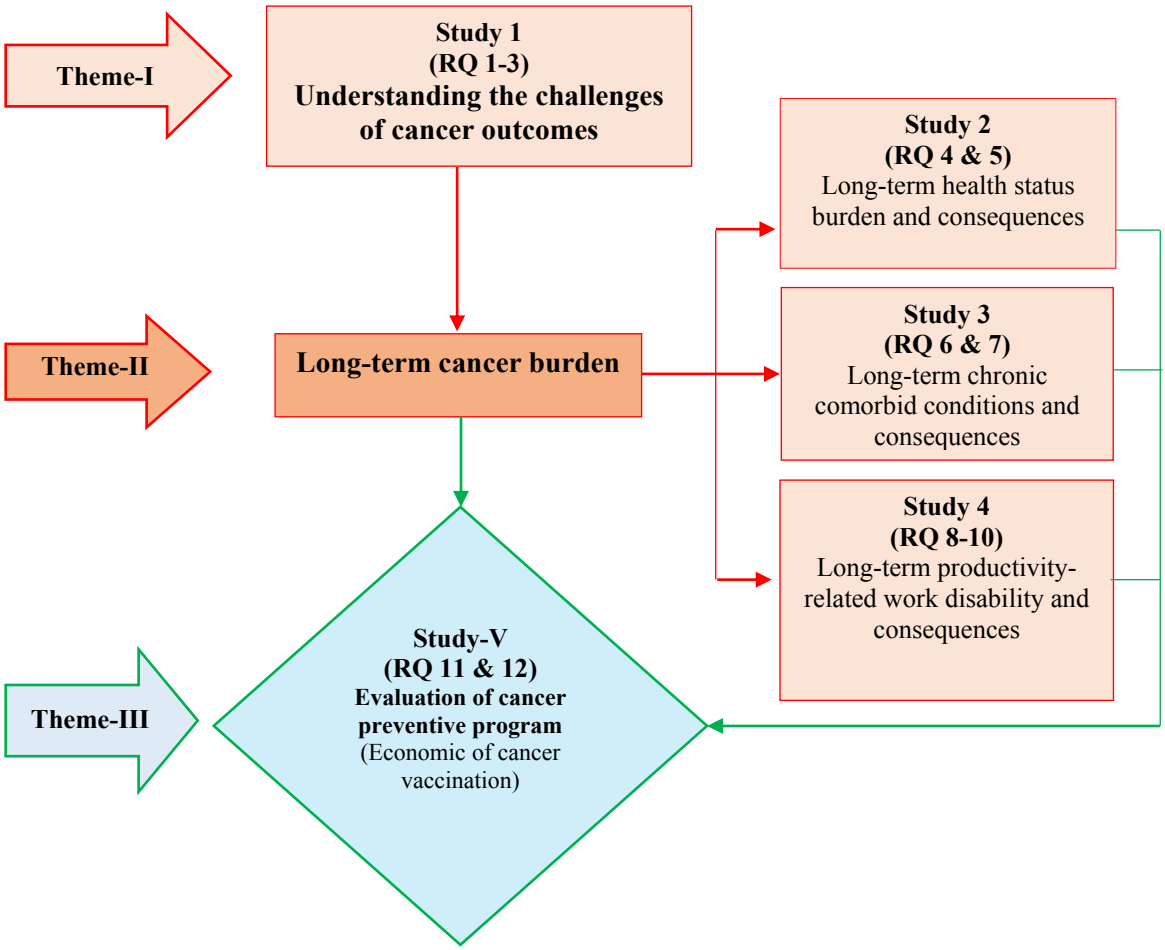

Figure 1. Five studies of the thesis: the interlinkages

Table 1. Summary facts about different studies objectives, research questions and conceptual issues

Study	Published paper(s)	Objective(s)	Research questions (RQs)	Conceptual issues	Study design/ approach/ perspective	Data sources	Outcome parameters
Study 1	Article-I	i) To examine the trends of cancer outcomes and associated burden over an identified periods.	RQ_1: What is an emerging trends of cancer outcomes in terms of incidence, mortality, hospitalisation and associated burden over identified periods?	Extend of the challenges of cancer outcomes: Incidence, mortality, hospitalisation and associated burden.	Incidence-based approach, health system perspective	AIHW	Cancer incidence, cancer-related mortality, hospitalisations, cancer burden (e.g., YLL, YLD, DALYs).
		ii) To measure the magnitude of socioeconomic inequalities in terms of cancer outcomes and cancer burden.	RQ_2: What is the magnitude and direction of the cancer outcomes and associated burden in terms of socioeconomic inequalities?				
		iii) To investigate associated determinants on cancer burden over an identified period.	RQ_3: What factors associate to health burden of cancer over an identified period?				
Study 2	Article-II	i) To examine the longitudinal nature of health status burden among cancer patients.	RQ_4: What is the longitudinal nature of health outcomes and the extent of health status burden among cancer patients in Australia?	Impact of long-term health status cancer burden and consequences.	Mixed longitudinal design	HILDA	Health status burden and associated determinants of health status burden.
		ii) To determine the factors that predict their health status burden over an identified period.	RQ_5: How does life style factors impact on health status burden of cancer survivors in Australia?				

(Continued)

Table 1. Summary facts about different studies objectives, research questions and conceptual issues (Continued)

Study	Published paper(s)	Objective(s)	Research questions (RQs)	Conceptual issues	Study design/ approach/ perspective	Data sources	Outcome parameters
Study 3	Article-III	i) To investigate the longitudinal distribution of chronic comorbid conditions among cancer survivors over an identified period.	$RQ_{6:}$ What is the longitudinal distribution and changes of chronic comorbid conditions with cancer survivors over times?	Impact of long-term burden of chronic comorbid conditions among cancer survivors and consequences.	Mixed longitudinal design	HILDA	Burden of chronic comorbid conditions and associated predictors
		ii) To identify the potential predictors of chronic comorbid conditions over an extended period.	$RQ_{7:}$ What factors influence the chronic comorbid exposure of cancer patients over an extended period of 2007 to 2017?				
Study 4	Article-IV	To examine the longitudinal impact of health burden on the magnitude of work-related disability of cancer survivors in Australia over an extended period of 2003-2017.	$RQ_{8:}$ What is the magnitude of work disability levels among cancer patients in Australia?	Impact of long-term productivity-related work disability and Consequences	Mixed longitudinal design	HILDA	Disability status and severity of disability and influencing determinants.
			$RQ_{9:}$ What is the longitudinal association between health burden and the magnitude of work disability among cancer patients in Australia over 2003-2017?				
			$RQ_{10:}$ What are the potential predictors associated with the magnitude of work disability for cancer patients in Australia over this extended period?				
Study 5	Article-V	i) To extend and mapping of the general trends on the ongoing cost-effectiveness evaluation of the 9-valent HPV vaccination within a global context.	$RQ_{11:}$ To what extent of the ongoing cost-effectiveness evaluation of the 9-valent HPV vaccination performs in the global context?	To investigate the current evidence on the economic viability of HPV vaccination, from the global context	Systematic review	Relevant academic published articles	ICER per cancer cases averted, life saved, life year saved, DALYs averted.
	Article-VI	ii) To assess the cost-effectiveness of adding a nonavalent new Gardasil-9® (*9vHPV*) vaccine to the national immunisation schedule in Australia across three different delivery strategies.	$RQ_{12:}$ Is cancer vaccination economically viable to prevent cervical cancer in Australia?	To evaluate the cancer prevention strategy in terms of economically viable of cancer vaccination in Australia.	CEA from Health system and societal perspectives	National and international sources, relevant published articles	ICER per cancer cases averted, life saved, life year saved, DALYs averted.

AIHW = Australian Institute of Health and Welfare, HILDA = Household, Income and Labour Dynamics in Australia, CEA = Cost-effectiveness analysis, YLL = Years life lost, YLD= Years lost due to disability, DALYs = Disability adjusted life years, ICER= Incremental cost-effectiveness ratio

1.10 Data sources and study population

In the context of Australia, the study population was ethnically, geographically, and socio-economically diverse. The *first study* was restricted by the availability of various cancer-related national-level data sources. Data on cancer incidence, mortality, and hospitalisation were extracted from the publicly accessible Australian Institute of Health and Welfare (*AIHW*) online data sources (AIHW, 2019a), and cancer-related published reports (AIHW, 2016b, 2019b). Cancer burden-related data was collected from the Australian Burden of Disease Study (*ABDS*). Data were retrieved from the published reports of *ABDS*-2011 and *ABDS*-2015, the last two reports that explicitly included cancer (AIHW, 2016b, 2019b). *Study I* used these national level accumulated data in its analytical exploration. A total of 2,784,148 registered cancer cases was accessed, based on data from 1982 to 2014 in Australia (see published article-I).

In *Studies 2-4*, data were accessed from the *HILDA* survey dataset (Summerfield *et al.*, 2018), which is a nationally representative longitudinal study of Australian households. Survey waves were selected based on the availability of data related to cancer and conceptual issues (Table 1). For example, *Study 2* used data from *HILDA* wave-13 in 2013 (n = 517) and wave-17 in 2017 (n = 576) to measure the longitudinal health status burden (see article–II). In *Study 3*, data were restricted to four waves (e.g., wave-7, wave-9, wave-13 and wave-17) based on the availability of data related to cancer (see published article-III). However, wave-3 was excluded from the analysis due to the limited data related to comorbidity status. A total of 2,066 diagnosed cancer patients were potential participants from the four waves: wave-7 in 2007 (n = 557), wave-9 in 2009 (n = 416), wave-13 in 2013 (n = 517) and wave-17 in 2017 (n = 576). *Study 4* was focused on productivity-related work disability among diagnosed cancer patients, and data were generated from five *HILDA* waves (505 patients from wave-3 in 2003, 557 patients from wave-7 in 2007, 416 patients from wave-9 in 2009, 517 patients from wave-13 in 2013 and 576 patients from wave-17 in 2017) (see published article-IV).

Finally, *Study 5* was constructed based on a full economic evaluation (i.e., cost-effectiveness analysis) of the cancer prevention program (new *9vHPV* cancer vaccination), from the global context (i.e., to investigate the current evidence on the economic viability of 9vHPV vaccination; see published article-V) and Australia (i.e., to evaluate the cancer prevention strategy in terms of economically viable of 9vHPV vaccination; see published article-VI). Data were derived from published original articles, secondary national and international data sources, and anecedotal evidence based on economic model input assumptions.

1.11 Theoretical underpinning

The essence of cancer burden is that it can be seen as a social dynamic, which can be explained with relevant theories and models. The findings of this thesis have been theorised inductively, which means the analytical exploration has been data-grounded, rather than theory-dictated. In this thesis, every finding was underpinned by a suitable theoretical framework. This theorising stage was not straightforward, but rather a reflexive process and the relevant theory was selected based on compelling arguments of the researchers. As a result of the response to reviewers' comments (the peer review process), however, the theoretical perspective was excluded from some of the papers in order to address the reviewers' comments. In this thesis, three inductively generated theories were adopted: social conflict theory (*Study 1*), stress-coping theory (*Studies 2-4*) and portfolio theory perspectives (*Study 5*). The following section outlines the reasons for selecting those theories.

1.11.1 Social conflict theory

One of the studies (*Study 1*) was performed to examine the national level cancer outcomes in terms of trends, determinants and inequality over the last three decades, through the prism of social conflict theory (Marx and Engels, 1848), which was used to explain the phenomenon of socioeconomic inequality as a driving force behind cancer outcomes. Social conflict theorists

argue that social classification emanates in a society from the conflict between and amongst social groups. In the mid-19th century Karl Marx was one of the principal social theorists who claimed that the attributes of the capitalist economy underpin upper-class domination of the socio-economic stratum (Marx, 1887). One of the striking themes in social conflict theory is that socioeconomic inequality is magnified owing to inequalities in age, race, wealth, gender, and geographical distribution. In this research (*Study 1*), social conflict theory fits into two dimensions. *First*, Australia has significant geographical differentiation, which indicates a deep divide among people in different localities in terms of their social capital, income, wealth, and class. This might generate systematic social conflict between the 'haves' and 'have nots'. *Second*, urban patients can more easily access health care services than those in remote areas. Other researchers have also used this theory to study different dimensions of social and health service provision (Sage Editors, 1957; Azar and Farah, 1981; Cornfield, 1991; Scambler, 2001; Hammack *et al.*, 2018).

1.11.2 Stress-coping theory

The theoretical framework of stress-coping theory was designed by Lazarus and colleagues (Lazarus and Folkman, 1984; Lazarus, 1999) to investigate which antecedent factors may be aligned with long-term cancer health status burden (*Study 2*), chronic comorbid conditions (*Study 3*), and productivity-related work disability (*Study 4*). The longitudinal study perspective was underpinned by a stress-coping theory in order to determine if it could predict long-term health status burden (Dunn *et al.*, 2013), chronic comorbid conditions (Hermsen *et al.*, 2016), and work-related disability (Martz and Livneh, 2007; Livneh, 2015) over an extended period. They investigated individuals who faced the burden of life-threatening cancer and examined the magnitude of the cancer burden associated with its initial appraisal as well as their ability to manage the secondary stage of treatment and progression. In terms of secondary appraisal, individuals reconsidered their health status based on the magnitude of the burden (as either more or less). The theory of stress-coping is that the burden which extends over an extended period of

time adversely affects health outcomes, including cancer outcomes (Lazarus, 1999). Furthermore, the theory holds that the magnitude of burden related to the disease is contextual, meaning that it involves a transaction between the individual and the management of disease, and it is a process, meaning that it changes over time.

To examine the longitudinal effects of the model, it is hypothesised that several antecedent variables (e.g., individual characteristics, social factors, and disease-related factors), measured at the symptom-level, might predict outcome factors (appraisal of disease with comorbidities, course of treatment, caregiving, life condition, uncertainty, disability). Moreover, the combination of factors (e.g., antecedent and outcomes) was assumed to predict patients' health burden. In this context, the stress-coping theory fits with two adaptive tasks common across situations that threaten physical well-being managing the burden of disease and coping with a changing reality.

1.11.3 Portfolio theory

Portfolio theory, as applied in health economics, highlights the trade-offs that exist between the returns on investment in healthcare interventions or programs (e.g., cancer vaccination) and the risk associated with the outcomes (both costs and effects) (Markowitz, 1952). This theory also suggests a means to improve the risk-return characteristics of investments in healthcare interventions or programs (e.g., cancer vaccination) through change when costs and outcomes are uncertain. The foundation of this theory is based on the potential assumption that the investment proportions are not subject to uncertainty and that the budget can be invested in healthcare interventions or programs. Furthermore, a portfolio approach allows one to evaluate a combination of healthcare interventions or associated programs, focusing on their returns (e.g., health benefits) and risk related to outcomes. While various methods have been suggested for incorporating risk in the evaluation of costs and outcomes in health economic evaluations (Zivin and Bridges, 2002), these techniques remain dependent on the specification of a threshold incremental cost-effectiveness ratio for decision-making from the health

system and societal perspectives. In this thesis, *Study 5* is underpinned by the essence of Portfolio theory, whereas previous researchers have employed this theory to study healthcare interventions through economic evaluation approaches (Zivin and Bridges, 2002; Sendi *et al.*, 2003, 2004; Bridges and Terris, 2004; Gafni, 2006).

1.12 Conceptual framework of the thesis

The conceptual framework (Figure 2) of the thesis explains the proposed hypotheses, which have explored the direct or indirect relationships that exist between individual, demographic, environmental and other associated factors, and cancer outcomes. These factors have a fundamental relationship with the risk of developing cancer. Consequently, cancer leads to a huge health and economic burden. Different factors may be contributing, at different levels, to the degree of inequality of cancer outcomes. These relationships have been examined in the proposed model, and the burden of cancer was considered as a consequence of the disease. Different dimensions of health status have previously been shown to influence health-related behaviour. As a result, cancer patients are exposed to adverse events leading to reduced health status. Cancer leads to a huge economic burden on the individual and households, as well as society.

The distribution of comorbidity varies by patient-level factors. Like cancer itself, comorbidity increases with age. Functional status, a measure of patients' ability to perform everyday activities, is related to both the presence and the consequences of chronic comorbid conditions. Health status burden is associated with increased vulnerability to stressors that result from decreased health status as well as physiological strength (Fried *et al.*, 2004). Furthermore, health status burden is strongly associated with increased age and the severity of the disease. In the context of comorbidity experiences, patients assess their health status depending on the severity of disease (as either 'better' or 'worse') (Lazarus, 1999). Despite strong associations between them, comorbidity, functional status, and health status burden are separate entities, and each has an independent effect on outcomes (Fried *et al.*, 2004). To investigate the longitudinal effects, it was assumed that several

predictors (e.g., individual background characteristics, social factors, and disease-related symptomatic factors), measured at the symptom-level, might predict outcome factors (e.g., appraisal of disease severity levels, utilisation of advanced treatment, life satisfaction, and uncertainty). Moreover, the combination of predictors was expected to predict patients' health outcomes (e.g., chronic comorbid conditions, long-term health problems or disability, and adverse events).

Considering the economic burden, the long-term impacts include out-of-pocket payments, catastrophic expenditure, work-related disability, lost productivity, reduced income, and increased costs to the health system (Figure 2). The benefit of developing this structure for analytical assessment resides in the establishment of a logical model that indicates potential causal relationships among factors, thus enabling the implementation of specific policies related to cancer. A positive feature of the framework is the opportunity to investigate the costs and societal benefits of cancer prevention programs (e.g., cancer vaccination) (Figure 2). To examine the degree of inequality in relation to cancer, this study employed inequality related techniques referencing social conflict theory.

To inquire into the magnitude of long-term cancer burden and consequences on cancer outcomes and current challenges (Figure 2) in the Australian health system (*Study 1*), health status burden (*Study 2*), chronic comorbid condition (*Study 3*), and productivity-related work disability (*Study 4*), this research employed a mixed-longitudinal approach using advanced inequalities related techniques and statistical models (e.g., generalized linear mixed models, fixed-effect negative binomial regression model and fixed-effect multinomial logistic regression model), underpinned by stress-coping theory. Finally, to evaluate a cancer control program (cancer vaccination), in terms of its societal benefits and associated costs, a full economic evaluation (e.g., cost-effectiveness analysis) was performed, which is also aligned with portfolio theory (*Study 5*).

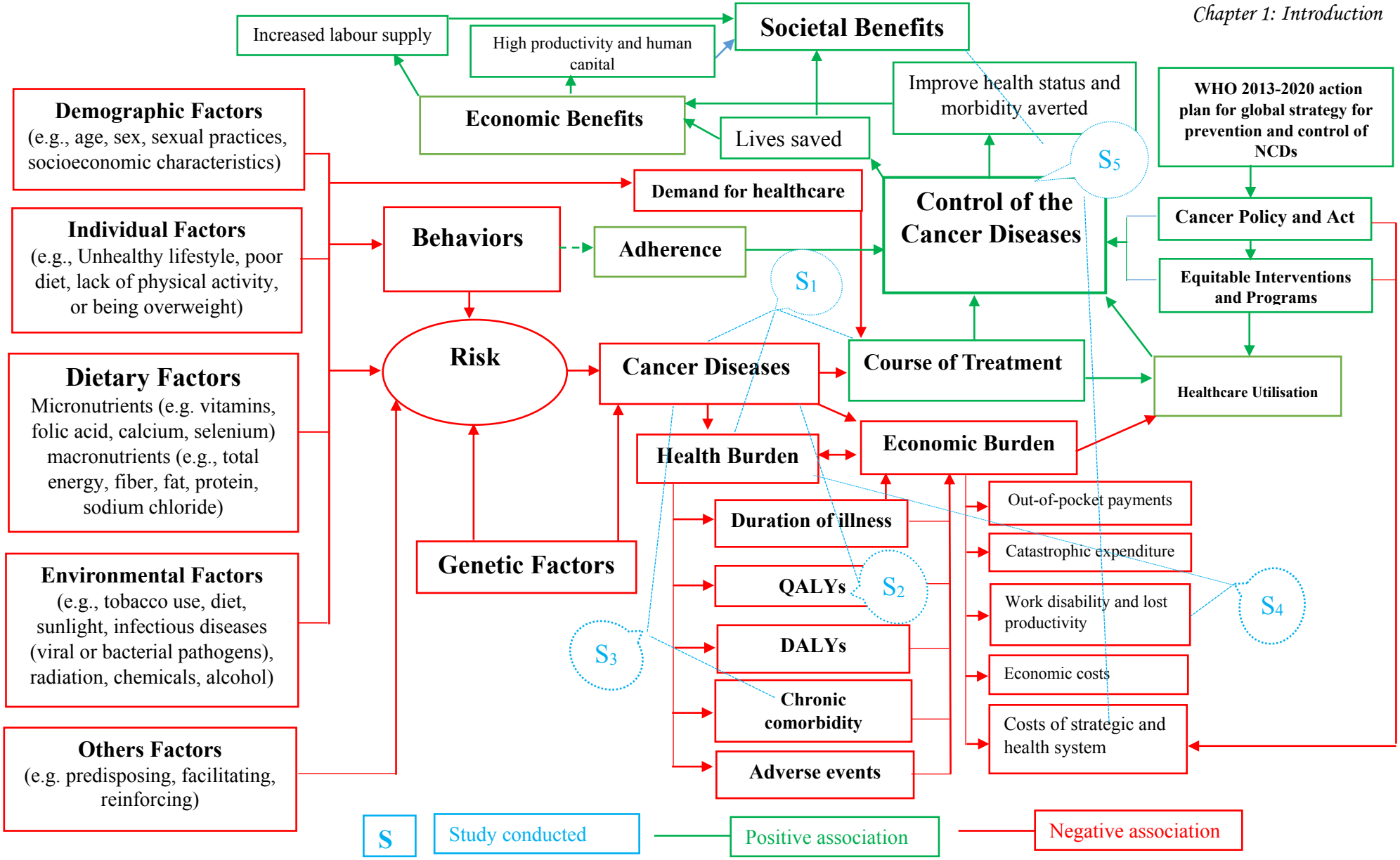

Figure 2. Conceptual framework of the thesis

1.13 Thesis organisation

This thesis is composed of an introduction that highlights the research theme, a review of the literature that identifies the gap in the existing evidence, five major studies that cover the objectives, a discussion and conclusions as well as future research, which summarises the findings and contributions of this study. A total of six (Quartile Q1) journal articles produced from this research are presented below:

Article from study 1:

- **Article I**

  Rashidul Alam Mahumud*, Khorshed Alam, Jeff Dunn, Jeff Gow. Emerging cancer incidence, mortality, hospitalisation, and associated burden among Australian cancer patients, 1982-2014: An incidence-based approach in terms of trends, determinants and inequality. *BMJ Open* 2019; 9(12): e031874. (Quartile-1 ranked; Impact Factor: 2.376; SJR = 1.321; SNIP = 1.145; Publisher: BMJ Publishing Group).
  DOI: http://dx.doi.org/10.1136/bmjopen-2019-031874

Article from study 2:

- **Article II**

  Rashidul Alam Mahumud*, Khorshed Alam, Jeff Dunn, Jeff Gow. The impact of lifestyle risk factors, life satisfaction and chronic exposure on changing in longitudinal health status burden among Australian cancer patients, 2013-2017. *BMJ Open* (under review) (Quartile-1 ranked; Impact Factor: 2.376; SJR = 1.321; SNIP = 1.145; Publisher: BMJ Publishing Group).
  Ref. No.: bmjopen-2019-036675

Article from study 3:

- **Article III**

  Rashidul Alam Mahumud*, Khorshed Alam, Jeff Dunn, Jeff Gow. The burden of chronic diseases among Australian cancer patients: Evidence from a longitudinal exploration, 2003-2017. *PLoS ONE*

2020*;* 15(2): e0228744. (Quartile-1 ranked, Impact Factor: 2.392; SJR = 1.100; SNIP = 1.123; Publisher: Public Library of Science).

DOI: https://doi.org/10.1371/journal.pone.0228744

Article from study 4:

- **Article IV**

  Rashidul Alam Mahumud*, Khorshed Alam, Jeff Dunn, Jeff Gow. The changing relationship between health burden and work disability of Australian cancer survivors, 2003-2017. *BMC Public Health* 2020; 20 (548): 1-14 (Quartile-1 ranked, Impact Factor: 2.567; SJR = 1.382; SNIP = 1.342; Publisher: Springer Nature).

  DOI: https://doi.org/10.1186/s12889-020-08710-9

Articles from study 5:

- **Article V**

  Rashidul Alam Mahumud*, Khorshed Alam, Syed Afroz Keramat, Gail M Ormsby, Jeff Dunn, Jeff Gow. Cost-effectiveness evaluations of the 9-Valent human papillomavirus (HPV) vaccine: Evidence from a systematic review. *PLoS ONE* 2020; 15(6): e0233499. (Quartile-1 ranked, Impact Factor: 2.392; SJR = 1.100; SNIP = 1.123; Publisher: Public Library of Science).

  DOI: https://doi.org/10.1371/journal.pone.0233499

- **Article VI**

  Rashidul Alam Mahumud*, Khorshed Alam, Jeff Dunn, Jeff Gow. The cost-effectiveness of controlling cervical cancer using a new 9-valent human papillomavirus vaccine among school-aged girls in Australia. *PLoS ONE* 2019; 14(10): e0223658. (Quartile-1 ranked, Impact Factor: 2.392; SJR = 1.100; SNIP = 1.123; Publisher: Public Library of Science).

  DOI: https://doi.org/10.1371/journal.pone.0223658.

For a better understanding of the link among the studies and articles, the flow of the thesis is graphically presented in Figure 3.

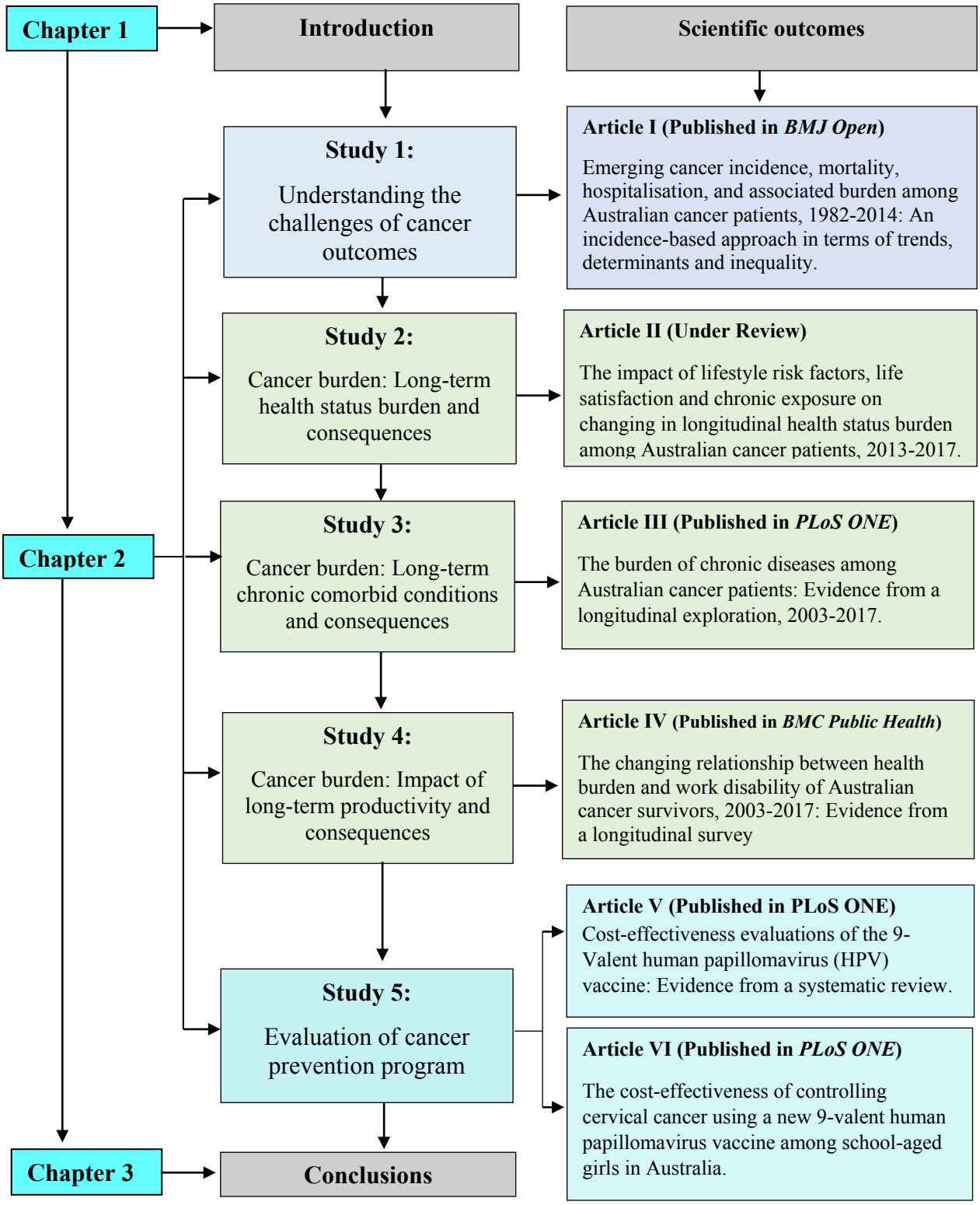

Figure 3. Flow diagram of the thesis structure

1.14 References

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Chapter-2:
Conducted Empirical Studies 1-5

2.1 Study 1

Challenges of cancer diseases: Incidence, mortality, hospitalisation and associated burden

The *first study* of this thesis examined the national level cancer outcomes in Australia and considered an incidence-based approach in terms of trends, determinants and inequality over the last three decades. Study 1 provides evidence of understanding the challenges of cancer outcomes, which is significant for routine oncology follow-ups to explore how cancer survivors' characteristics impact on their health status outcomes over an extended period.

Article I: Emerging cancer incidence, mortality, hospitalisation and associated burden (years lost life, years lost due to disability, disability-adjusted life years) in Australia, 1982-2014: Evidence from an incidence-based study in terms of trends, determinants and inequality

The objective of *Study 1* was to understand the trends, determinants and magnitude of socioeconomic inequality associated with cancer incidence, hospitalisation, mortality and its burden over the period 1982 to 2014 in Australia using an incidence-based approach. This study found that cancer incidence, hospitalisation, cancer-related mortality, and burden of cancer all increased significantly over the period. Furthermore, survival inequality was most pronounced for cervix, prostate, melanoma, Non-Hodgkin Lymphoma, and breast cancers. Furthermore, socio-economically disadvantaged people were more likely to bear an increasing cancer burden in terms of incidence, mortality, and death. This study concludes that significant differences in the burden of cancer persist across socio-economic strata in Australia. Policymakers should therefore introduce appropriate cancer policies to provide universal cancer care, which could reduce this burden by ensuring curable and preventive cancer care services are made available to all people.

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Emerging cancer incidence, mortality, hospitalisation and associated burden among Australian cancer patients, 1982 – 2014: an incidence-based approach in terms of trends, determinants and inequality

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ABSTRACT

Objective Cancer is a leading killer worldwide, including Australia. Cancer diagnosis leads to a substantial burden on the individual, their family and society. The main aim of this study is to understand the trends, determinants and inequalities associated with cancer incidence, hospitalisation, mortality and its burden over the period 1982 to 2014 in Australia.

Settings The study was conducted in Australia.

Study design An incidence-based study design was used.

Methods Data came from the publicly accessible Australian Institute of Health and Welfare database. This contained 2 784 148 registered cancer cases over the study period for all types of cancer. Erreygers' concentration index was used to examine the magnitude of socioeconomic inequality with regards to cancer outcomes. Furthermore, a generalised linear model was constructed to identify the influential factors on the overall burden of cancer.

Results The results showed that cancer incidence (annual average percentage change, AAPC=1.33%), hospitalisation (AAPC=1.27%), cancer-related mortality (AAPC=0.76%) and burden of cancer (AAPC=0.84%) all increased significantly over the period. The same-day (AAPC=1.35%) and overnight (AAPC=1.19%) hospitalisation rates also showed an increasing trend. Further, the ratio (least-most advantaged economic resources ratio, LMR of mortality (M) and LMR of incidence (I)) was especially high for cervix (M/I=1.802), prostate (M/I=1.514), melanoma (M/I=1.325), non-Hodgkin's lymphoma (M/I=1.325) and breast (M/I=1.318), suggesting that survival inequality was most pronounced for these cancers. Socioeconomically disadvantaged people were more likely to bear an increasing cancer burden in terms of incidence, mortality and death.

Conclusions Significant differences in the burden of cancer persist across socioeconomic strata in Australia. Policymakers should therefore introduce appropriate cancer policies to provide universal cancer care, which could reduce this burden by ensuring curable and preventive cancer care services are made available to all people.

Strengths and limitations of this study

- This study examined the trends, determinants and inequality in terms of incidence, mortality, hospitalisation and associated burden of cancer (eg, years life lost, years lost due to disability and disability-adjusted life years) in the Australian context over a 33 year period.
- This study was not captured in details inequalities regarding the cancer survivorship in terms of stage, treatment procedures and utilisation of healthcare.
- Although we have limited understanding of what is driving these changes in cancer outcomes as reported here they may reflect random variation or changes in unknown risk factors, and therefore highlight the need for more research into the aetiology of cancer.

BACKGROUND

Non-communicable diseases (NCDs) are accountable for the majority of global deaths.[1] Cancer is expected to rank as the most significant global public health problem and a leading cause of death and illness in the world in the 21st century[2–6] including Australia.[7] In 2019, it is estimated that almost 145 000 new cases of cancer will be diagnosed in Australia, and 35% of these individuals will eventually die from the disease.[7] Cancer accounts for the highest burden of disease of any illness, at approximately 18% (19% for males; 17% for females), followed by cardiovascular disease (14%), musculoskeletal (13%) and mental health (12%).[8] Approximately 40% of cancer patients are of working age in Australia.[7] Among those in employment, 46% are unable to return to work after an episode,[9] and 67% return to employment or change their job after being diagnosed.[10] The majority of

cancer survival patients depend on family, relatives and friends for physical and economical support during their treatment and/or in the last stages of the disease.[9–12] Cancer-related illness results in a substantial number of patients experiencing economical hardship due to high out-of-pocket expenses (eg, medicines and treatments, including diagnostics), lost productivity, loss/reduction of household income and other induced expenditure.[9 10 12 13] The economic burden of cancer is of growing concern for policymakers, healthcare practitioners, physicians, employers and society overall.[10 12] Furthermore, the magnitude of the cancer burden increases significantly with remoteness from treatment sources and those individuals in depressed socioeconomic circumstances.[14–16] Considerable progress has been made in recent decades in terms of cancer survival and reduced mortality rates[17 18] through several initiatives including introducing primary preventive strategies and effective collaboration with non-government organisations and other stakeholders. Therefore, a reduction of cancer incidence, along with improvements in cancer treatments and therefore survival rates, are essential to reduce the burden of the disease.

Economic disparities between socioeconomically advantaged and disadvantaged individuals and groups are worsened by the increasing burden of cancer in Australia.[15] The lack of appropriate services are significantly worse in resource-poor settings, including geographically disadvantaged areas compared with more advantaged people and communities with easier access to a greater range of cancer services, increased knowledge and awareness of cancer prevention and better and more easily accessible health facilities and resources.[15 19 20] Other common reasons for such disparities include limited affordability and accessibility of cancer care services for individuals from socioeconomically disadvantaged groups,[16] and their inadequate utilisation of healthcare.[21] Thus, increased cancer incidence leads to a higher overall burden for the individual, family and society, which is exacerbated for the more disadvantaged.

In the recent past, disparities related to cancer outcomes have become the subject of international focus and new service initiatives.[2 6] In 2016, the WHO Executive Board recommendation was to strengthen health systems to ensure early detection and diagnosis, as well as accessible, affordable and appropriate and quality healthcare services for all patients with cancer.[22] Only a few studies have focused explicitly on socioeconomic inequality of cancer care and healthcare utilisation in Australia. This study therefore purposes to provide data and analysis on trends in cancer incidence, mortality rates, hospitalisation and associated burden (years life lost, YLL; years lost due to disability, YLD and disability-adjusted life years, DALYs) for the most prevalent malignancies among Australians, by sex, state, remoteness and socioeconomic status, using routinely collected health data for the period of 1982 to 2014.

There is an extensive body of research on the many different dimensions of cancer. In recent decades, the cancer incidence has increased,[5 17 23–25] which has been more pronounced among adolescents and young adults,[26] and older adults,[27] yet cancer-related mortality rates have slightly dropped.[28] Some types of cancer in Australia are the highest in the world: melanoma,[26] keratinocyte and melanocyte.[29] Australia and New Zealand together have the highest rates for Merkel cell carcinoma.[30 31] A number of studies have focused on geographical or socioeconomic disparities in cancer care and survival.[32–38] These have usually been conducted in small settings at the Australian state level. No previous studies have attempted to measure the trends, associated determinants and magnitude of socioeconomic inequalities of cancer outcomes (eg, incidence, mortality, hospitalisation and burden of cancer - YLL, YLD, DALYs) over time. Therefore, national level trends, the differential socioeconomic inequality of cancer outcomes, as well as influential factors associated with the cancer burden in Australia are unclear.

Furthermore, the study's findings will provide authorities with national evidence about the trends and magnitude of the inequalities in cancer burden and hopefully assist in developing low-cost interventions to reduce this burden. This study thus aims to examine the trends, associated determinants and magnitude of socioeconomic inequality as related to incidence, mortality, YLL, YLD and DALYs, as a result of cancer.

METHODS

Study design

An incidence-based approach was used to examine the trends and socioeconomic inequalities associated with adverse cancer outcomes in Australia. A health system perspective was adopted and cancer-related data were accessed from organisations that are committed to promote, restore or maintain health and well-being.[39 40] The study population represented different population subgroups using characteristics such as sex, geographical distribution and economic circumstances.

Australian health system

Australian health system (AHS) provides quality and affordable healthcare services for all Australians. It is operated by three levels of government: federal (financing), state and territory (funding and service delivery) and local (service delivery).[41] The foundation of AHS is the publically funded national universal health insurance scheme, Medicare and its predecessor Medibank which commenced in the 1970s to promote universal healthcare by providing safe and affordable healthcare services for Australians. Through Medicare, patients are able to access medical services, treatment in public hospitals free of charge, receive subsidised out of hospital treatment and medicines. Those eligible to access healthcare services through Medicare include: Australian and New Zealand citizens, permanent residents of Australia and individuals who have applied for a permanent visa.[42] On the other hand, overseas student health cover is mandatory for all

international students, to ensure they and their dependents can access affordable healthcare while living and studying in Australia. Patients are provided a rebate benefit for healthcare services for out of hospital services.

The rebate amount is case dependent. For example, for a consultation with a general practitioner (GP), specialist or consultant physician of at least 10 min duration on a patient with cancer to develop a multidisciplinary treatment plan, the schedule payment is $A81.50 in 2019, and the benefit is 100% of the schedule fee; hyperbaric oxygen therapy associated with treatment of localised non-neurological soft tissue radiation injuries has a schedule fee of $A254.75 and the benefit is 75% of the schedule fee, or $A191.10.[42] While public hospitals are free of charge, the majority of out of hospital healthcare services are provided by private health providers. The actual amount of fees for service is set by the providers themselves and are not regulated, meaning that private healthcare providers can make their fees above the schedule payment. Any difference between the amount of the providers fee for a service and the amount of rebate is paid by the patient from their out-of-pocket (OOP). For example, if the actual amount charged of a provider is $A81.50 for a diagonostic (eg, blood) test, Medicare would provide a rebate of $A69.30 (75% of the schedule fee), leaving the patient to pay $A12.20. Medicare has additional policies to protect patients from catatrophic OOP healthcare payments. In this context, healthcare cards are provided to welfare recipients and low income earners, and other eligible patients who pay a lower OOP payment for prescription medicines.[43] The 'Medicare Safety Net' and 'Extended Medicare Safety Net' Programmes also provide higher rebates if an individual or family group reaches a certain level of total expenditure on OOP fees within a calendar year. Any subsequent services or prescriptions will have a higher proportion subsidised for the rest of that calendar year.[44] Under the 'Medicare Safety Net', once the threshold is reached then 100% of the schedule fee for all healthcare services is rebated; and under the 'Extended Medicare Safety Net' 80% of the actual OOP payments are rebated.[45]

Data sources

Various cancer-related national data sources were accessed. Data on cancer incidence, mortality and hospitalisation were extracted from the publicly accessible Australian Institute of Health and Welfare (AIHW) online database[7] and cancer-related published reports.[8 46] AIHW accumulates data from the Australian Cancer Database (ACD), National Mortality Database (NMD) and National Hospital Morbidity Database (NHMD). ACD accumulates and manages all sorts of cancer data from each Australian state and territory under legal mandate since 1982. Different types of hospitals (eg, government and non-government), clinics, laboratories other organisations and institutions are required to report all cancer cases to the central cancer registry (CCR). The CCR data is delivered to the AIHW on an annual basis, where it is accumulated into the ACD. The NMD includes information supplied by the registries of births, deaths and marriages and the national coronial information system. These data are then coded by the Australian Bureau of Statistics (ABS) and are incorporated into the NMD. The NHMD is an accumulation of episode-level records of hospitalised patient morbidity data collection systems (eg, all acute and psychiatric hospitals, freestanding day hospital facilities and alcohol and drug treatment centres). Further, cancer burden-related data is collected via the Australian Burden of Disease Study (ABDS). Data were retrieved from the published reports of ABDS-2011 and ABDS-2015, the last two that explicitly included cancer.[8 46] Death caused by cancer was considered as the fatal burden (eg, YLL) and this data was sourced from the NMD. The non-fatal cancer burden related data emanated from different administrative sources including NHMD, ACD, NMD and some epidemiological studies. ABDS amassed data on some other parameters from the Global Burden of Disease studies of 2010 and 2013 that covered the standard life table for fatal burden (YLL), health status and disability weights for the non-fatal burden (YLD) and relative risks and the risk factor attribution.[8 46] The present study used these national level accumulated data in the analysis.

Study population

A total of 2 784 148 registered cancer cases (male=1 537 882; female=1 246 265) were accessed, based on data from 1982 to 2014 in Australia (table 1). In addition, to revealing the trends of cancer-related mortality over the same period, a total of 1 165 552 cancer-related deaths (male=659 105; female=506 447) were considered. Due to the paucity and availability of data related to cancer outcomes, a total of 591 631 registered cancer cases during the period from 2008 to 2012 and a total of 217 349 cancer-related deaths during 2010 to 2014 were used to examine inequality in cancer incidence and cancer-related mortality in Australia.

Measurement of cancer parameters

The age-standardised cancer incidence, or mortality rate, was measured using the number of new cases diagnosed or deaths for a specific age group, divided by the mid-year population of the same age group and year. Similarly, cancer incidence or mortality rate was estimated from the total number of new cases diagnosed or deaths across all age groups combined, divided by the mid-year population. These rates were interpreted as the number of new cases of cancer or deaths per 100 000 population. Cancer related burden estimation was undertaken using the burden of disease methodology.[8 46] In the ABDS, the burden of cancer was calculated through the DALY by summing up the fatal burden (ie, YLL) due to premature cancer-related mortality and the non-fatal burden (ie, YLD) for patients surviving the condition.

$$DALY = YLL + YLD \quad (1)$$

$$YLL = \frac{N}{r}(1 - e^{-rL}) \quad (2)$$

Table 1 Characteristics of the study parameters

Parameters	Conceptual issues	Sample population	Period	Data sources
Cancer incidence	To examine the trends of cancer outcomes	2 784 148	1982–2014	ACD
Cancer-related mortality		1 165 552	1982–2014	NMD
Cancer burden (eg, YLL, YLD, DALYs)		ABDS population	2011–2015	ABDS
Number of cancer-related hospitalisations		13 213 340	2000–2015	NHMD
Cancer incidence	To measure the magnitude of socioeconomic inequalities in terms of cancer outcomes and cancer burden	591 631	2008–2012	ACD
Cancer-related mortality		217 349	2010–2014	NMD
Cancer burden (eg, YLL, YLD, DALYs)		ABDS population	2011–2015	ABDS
Cancer burden (eg, YLL, YLD, DALYs)	To investigate associated determinants on cancer burden over the period	ABDS population	2011–2015	ABDS

ABDS, Australian Burden of Disease Study; ACD, Australian Cancer Database; DALYs, disability-adjusted life years; NHMD, National Hospital Morbidity Database; NMD, National Mortality Database; YLD, years lost due to disability; YLL, years life lost.

$$YLD = I \times DW \times L\left(\frac{1-e^{-rL}}{r}\right) \quad (3)$$

Where, n=number of deaths; L (YLL)=standard life expectancy at the age of death in that year; I=number of people with each type of cancer cases; DW=disability wt; r=discount rate; L (YLD)=duration of disability in years.

Definition of some potential factors

Index of economic resources

The magnitude of inequality in cancer outcomes was examined using an index of relative socioeconomic disadvantage (IRSD). The IRSD was developed by the ABS using potential factors like average household income, education level and unemployment rates.[47] It is a geographical area-based estimate of socioeconomic status where small geographical settings of Australia are categorised from economically disadvantaged to wealthy. This index is employed as a proxy for the socioeconomic status of the people living in different geographical settings in Australia. The cut-offs value for each of the quintiles are as follows: Q_1 (IRSD ≤927.0), Q_2 (927.0> IRSD ≤965.8), Q_3 (965.8> IRSD ≤1001.8), Q_4 (1001.8> IRSD ≤1056.0) or Q_5 (IRSD >1056.0).[47] The most disadvantaged socioeconomic quantile (Q_1) corresponds to geographical settings covering the 20% of the population with least advantaged socioeconomic areas, and the fifth quintile (Q_5) refers to the 20% of the population with the most advantaged socioeconomic areas.

Remoteness

Remote locations exist in each state and territory of Australia and are based on the accessibility to services and Remoteness Index of Australia, which is constructed by the Australian Population and Migration Research Centre at the University of Adelaide.[48] Remoteness was classified into six groups: major cities, inner regional, outer regional, remote, very remote and migratory. Migratory was excluded from the current analysis due to the paucity of information. The category of the major cities included Australia's capital cities, except Darwin and Hobart, which were treated as an inner regional.

Data analysis

Trend analysis

Trend analysis of cancer incidence, cancer-related mortality rates, hospitalisations and burden of cancer were performed using the ACD (from 1982 to 2014), NMD (1982 to 2014), NHMD (2000 to 2015) and ABDS (2011 to 2015) population data sets, respectively. Trend analyses were done across sex, state and socioeconomic status over these periods. To identify changes in cancer parameters trends, joinpoint regression analysis was performed using the Joinpoint Regression Programs, V.4.5.0.1.[49] The annual percentage change (APC) in rates between trend-change points (ie, joinpoint segment) was calculated, and it also estimated the average annual percentage change (AAPC) in the whole study period. A negative APC indicates a decreasing trend whereas a positive APC indicates an increasing trend. Furthermore, increased or decreased APC of cancer-related outcomes were examined by the magnitude of cancer's impact over the period.

To measure the APC, the following model was used:

$$log(Y_x) = b_0 + b_1 x \quad (4)$$

where, log (Y_x) is the natural logarithm of the rate in year x. Then, the APC from year 'x' to year 'x+1' was:

$$APC = \frac{e^{b_0+b_1(x+1)} - e^{b_0+b_1 x}}{e^{b_0+b_1 x}} \times 100 = \left(e^{b_1} - 1\right) \times 100 \quad (5)$$

Then, AAPC was estimated as a weighted average of the estimated APC in each segment by using the segment lengths as weights.

$$AAPC = \left(e^{\frac{\sum(S_i \times APC_i)}{\sum S_i}} - 1\right) \times 100 \quad (6)$$

where, S_i=i th segment lengths (i=1, 2, 3, …, n), APC_i=i th annual percentage change.

Measuring socioeconomic inequality

Index of Economic Resources (IER) was measured in quintiles, with the first quintile (Q_1) representing the lowest 20% of the total population living in the most impoverished socioeconomic areas, and the fifth quintile (Q_5) representing the top 20% of the total population living in the most prosperous socioeconomic areas. Inequality analyses were constructed for cancer incidence, cancer-related mortality and DALYs across the different IER quintiles. The absolute and relative differences (eg, least advantaged-most advantaged difference, LMD and least advantaged-most advantaged ratio, LMR) in cancer incidence, cancer-related mortality, YLL, YLD and DALY were calculated to examine the magnitude and direction of the cancer outcomes across different socioeconomic groups. A high value of the LMR and LMD represents a high degree of socioeconomic inequality.[16] The ratio of cancer mortality and incidence (M/I) was measured to capture the survival inequality of cancer patients. The measures of the concentration index (CI) (Erreygers' CI) was used to examine the magnitude of socioeconomic inequality and the trends in adverse cancer outcome changes during the period.[50]

Multivariate analysis

The fatal cancer burden (eg, YLL) was considered as the outcome variable in the analytical exploration. YLL is characterised by a large cluster of data and a right-skewed distribution, but the zero values were excluded from the analysis. The natural logarithm of YLL was used to reduce the effects of the skewed nature of the burden of cancer data. In the multivariate analysis, natural logged YLL was predicted using different patients' characteristics related to demographics (eg, sex), state, socioeconomic position and geographical distribution (eg, remoteness). A generalised linear model (GLM) was constructed to examine these associations. The model was tested for sensitivity by including and excluding specific variables and estimating the robust SEs. A series of diagnostic tests were performed, such as tests on the presence of heteroscedasticity, multicollinearity and omitted variables. The Breusch-Pagan/Cook-Weisberg test was used to check the presence of heteroscedasticity in the model. Variance Inflation Factor test was performed to examine the presence of multicollinearity. The Ramsey Ramsey Regression Equation Specification Error Test (RESET) test was to check if there is any omitted variable bias in the model. The outcome of the GLM analysis is presented as adjusted regression coefficients with robust SEs along with 95% CIs. Data management and all statistical analyses were performed using Stata/SE 13.0 (StataCorp, College Station, Texas, USA). A p value <0.05 was considered statistically significant.

Ethics

This study was conducted using the publicly accessible AIHW online data sources and cancer-related published reports. Ethical approval was not required from an institutional review board because the patient information was de-identified.

Patient and public involvement

Patient and public were not involved in the design or planning of this study.

RESULTS

Trends in cancer incidence and cancer-related mortality

The overall incidence of cancer among males significantly increased from 1982 to 1994, and then increased exponentially until 2014 (figure 1). The rate of cancer incidence among females also showed an increasing trend from 1982 to 2014. The cancer incidence rate increased from 1984 (2507 cases) to 1991 (3896 cases) in South Australia, after which the rate increased slightly during the period 1992 (3994 cases) to 2002 (4127 cases), and then increased again until 2014 (5392 cases). A similar trend was observed for males in New South Wales and Western Australia. A sharp reduction of cancer incidence was seen during 1994 (1333 cases) to 1997 (1100 cases), and the overall rate increased during 1998 to 2008 (1124 cases to 1889 cases) in Tasmania. In the Northern Territory and Australian Capital Territory, the incidence of cancer increased exponentially for both males and females throughout the period. The overall cancer-related mortality rate also increased for both males (eg, 5000 cases in 1982 to 8470 cases in 2014) and females (eg, 3952 cases in 1982 to 6490 cases in 2014) in New South Wales from 1982 to 2014. Further, a similar trend was observed for male and female in Victoria, Queensland, Western Australia, South Australia and Tasmania during the period 1982 to 2014 (figure 2). However, in the Northern Territory and Australian Capital Territory, little change from the trend was observed.

Distribution of average annual percentage change in cancer incidence and cancer-related mortality

Cancer incidence was measured as an AAPC over the period 1982 to 2014 (figure 3). Cancer incidence increased by an AAPC of 1.33% over the period 1982 to 2014, with the AAPC slightly higher for males 1.38% compared with females 1.29%. The highest AAPC was found in Northern Territory (2.57%), followed by the Australian Capital Territory (1.78%) and Western Australia (1.65%). In NewSouth Wales (NSW), the rate of cancer incidence increased steadily from 1982 to 1994 and then oscillated until 2013. Similarly, the percentage change of cancer incidence rate increased among females over time. Cancer mortality rate rose 0.76% from 1982 to 2014, and the mortality rate among females (0.78%) was slightly higher compared with males (0.73%). In the Northern Territory, cancer-related mortality rate was comparatively very high among males (1.98%), while

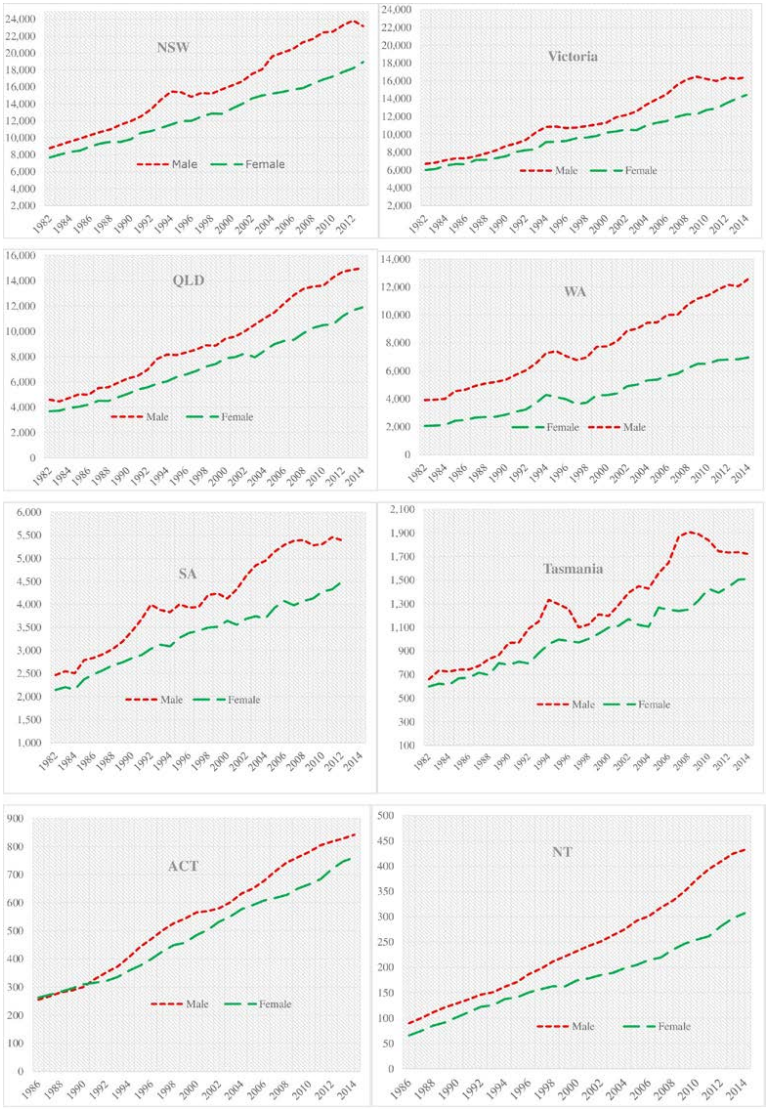

Figure 1 Trends of cancer incidence by sex and state, Australia, 1982 to 2014. ACT,Australian Capital Territory; NSW, New South Wales; NT, Northern Territory;QLD, Queensland; SA, South Australia; WA, Western Australia.

cancer-related mortality rates were found to be comparatively highest among females in Queensland (1.21%) and Australian Capital Territory (1.13%).

Trends in cancer-related hospitalisation

A total of 13 213 340 cancer-related hospitalisation cases were observed, of which 66.91% were for same-day treatment and 33.09% were overnight hospitalisations (figure 4). The AAPC of overall cancer-related hospitalisations increased by 1.27% as a whole, wherein same-day and overnight were 1.35% and 1.19%, respectively, higher over the period. The overnight hospitalisation rate fell over the period with a comparative increase in the same-day hospitalisation rate.

Trends in fatal cancer burden

An upward trend of the fatal burden of cancer was observed over the 2011 to 2015 period (figure 5). Males experienced a relatively higher burden (AAPC=0.89%) compared with females (AAPC=0.78%). The magnitude

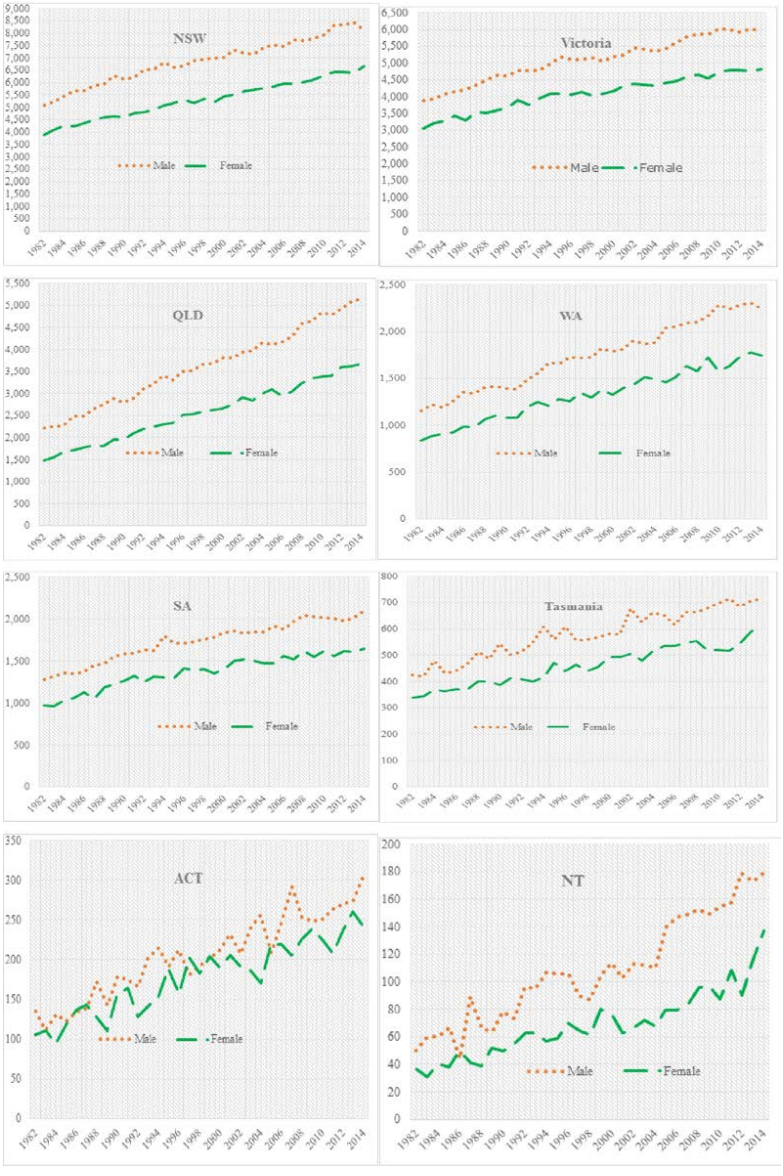

Figure 2 Trends of cancer mortality by sex and state, Australia, 1982 to 2014. ACT,Australian Capital Territory; NSW, New South Wales; NT, Northern Territory;QLD, Queensland; SA, South Australia; WA, Western Australia.

of the burden also varied across the states. For example, the rate of years of life lost increased by 9950 YLL (AAPC=1.16%) in Queensland, 2612 YLL (AAPC=0.22%) in NSW, 5838 YLL (AAPC=1.42%) in WesternAustralia, 2034 YLL (AAPC=0.63%) in SouthAustralia and 1253 YLL (AAPC=2.57%) in the AustralianCapital Territory. A major reduction in the fatal burden of cancer occurred among females (11 339 YLL, AAPC=−1.53%) in Tasmania and for males (3532 YLL, AAPC=−0.72%) in Victoria.

The magnitude of socioeconomic inequality for cancer patients

Cancer incidence was highest among the poorest quintile (table 2). Similarly, the age-specific cancer incidence

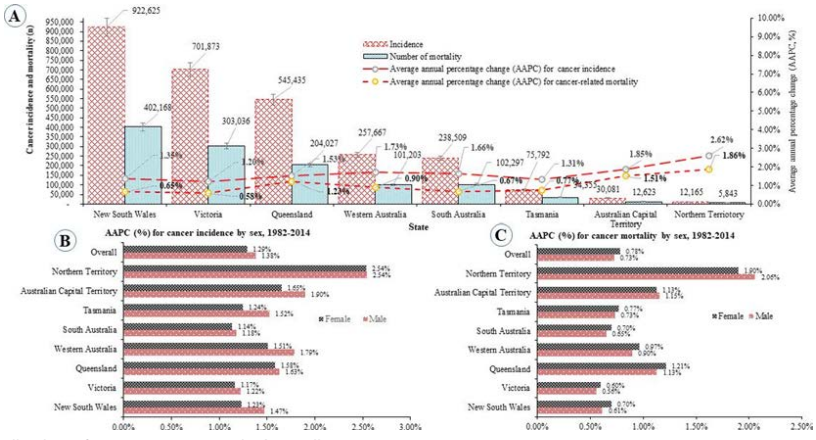

Figure 3 Distribution of cancer outcomes in Australia, 1982 to 2014.

was marginally highest among the poorest group. Furthermore, the poorest were 1.083 times more likely to be exposed to cancer than the richest and the poor/rich difference amounted to an additional 9873 cases per year. The cancer-related mortality rate difference was even starker with the LMR (1.513 times) and LMD (17 770 cases/100 000 persons). The overall ratio of (LMR of mortality) and (LMR of incidence) was high (M/I=1.276). Again, it has been revealed that nearly 34% more least advantaged group of people experienced cancer-related mortality compared with most advantaged economic resources of people. The overall magnitude of cancer incidence (CI=−0.029, p<*0.01*) and cancer-related mortality rate (CI=−0.011, p<*0.05*) were highest in the least advantaged group.

This skewed distribution was also true for the individual types or sites of cancer (table 3). The highest contributors to the socioeconomic inequality-mortality gap were colorectal (LMR=1.327 times), pancreas (LMR=1.336 times), lung (LMR=1.965 times), cervix (LMR=1.363 times), kidney (LMR=1.344 times), bladder (LMR=1.433 times) and unknown primary cancer (LMR=1.660 times). Further, the ratio (LMR of mortality) and (LMR of incidence) was especially high for cervix (M/I=1.802), prostate (M/I=1.514), melanoma (M/I=1.325), non-Hodgkin's lymphoma (M/I=1.325) and breast (M/I=1.318), suggesting that survival inequality was most pronounced for these cancers. The high value of the concentration index (CI) of different cancers, such as lung (CI=−0.060), melanoma (CI=−0.087), breast

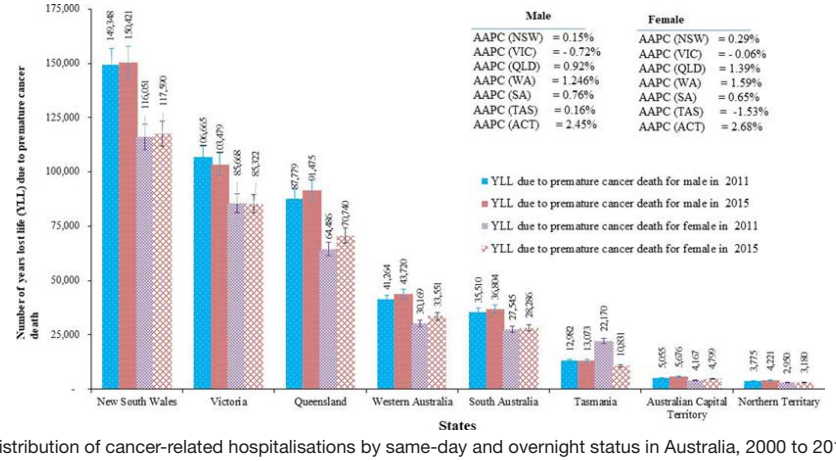

Figure 4 Distribution of cancer-related hospitalisations by same-day and overnight status in Australia, 2000 to 2015. AAPC, average annual percentage change; ACT, AustralianCapital Territory; NSW, New South Wales; NT, Northern Territory; QLD,Queensland; SA, South Australia; TAS, Tasmania; VIC, Victoria; WA, WesternAustralia.

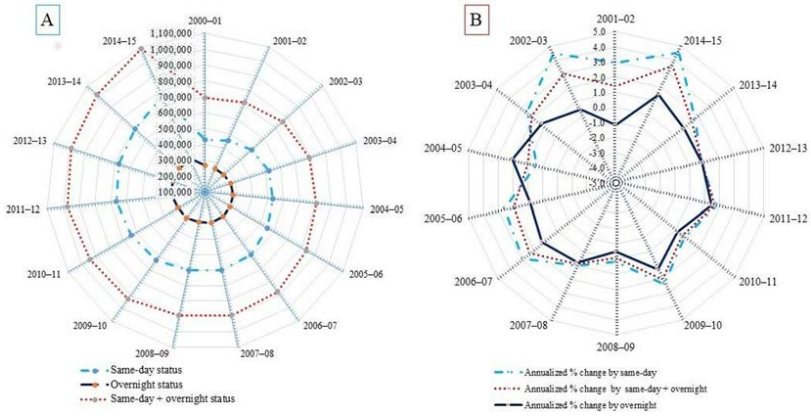

Figure 5 Trends of fatal burden of cancer across states, Australia, 2011 to 2015.

(CI=−0.104), prostate (CI=−0.076) and non-Hodgkin's lymphoma (CI=−0.078), indicates that cancer incidence was disproportionately distributed in the least economic resources quintile. In addition, a high degree of inequality in cancer related-mortality occurred across the different economic resources quintiles. Significant negative CI of mortality by different types of cancer, such as lung (CI=−0.066), melanoma (CI=−0.034), breast (CI=−0.048), cervix (CI=−0.095) and unknown primary cancer (CI=−0.043), reflected that mortality due to these types of cancers was more highly concentrated among the least advantaged economic resources group. Likewise, the number of deaths related to all types of cancer was highest among the least advantaged group. As a result, LMR is more than 1, and LMD is positive for all types of cancer-related mortality.

The magnitude of the fatal burden of cancer increases with a decline of the socioeconomic status of cancer patients (table 4). A notable difference was observed in the distribution of the fatal burden of cancer between the least advantaged and most advantaged quintiles. In 2011, people in the least advantaged quintile experienced high YLL (LMR=1.50 times, LMD=62.00 YLL/1000 persons) compared with the richest quintile, and it had increased again slightly by 2015 (LMR=1.57 times, LMD=66.00 YLL/1,000 persons). The annual rate of years of life lost declined constantly (AAPC=−0.87%) across different quintiles over the period, and the rate of reduction was greatest in the most advantaged quintile (AAPC=−1.69%) compared with the least advantaged quintile (AAPC=−0.63%). The fatal burden of all cancers was found to be highest in the least advantaged quintile (table 5). The annual reduction rate of cancer burden was highest in the most advantaged quintile compared with the least advantaged quintile. People diagnosed with cancer from the least advantaged economic resources areas bear a significant share of the total fatal burden (25%) compared with people from the most advantaged quintile (15%) (online supplementary appendix figure A1). However, a reduction in the share of fatal burden of cancer has been observed across all quintiles except the second quintile (AAPC=0.65% for Q_2).

Factors influencing the fatal burden of cancer

The regression coefficients were interpreted as the effect of a 1% change in the characteristics of cancer patients on the 1% change in YLL (table 6). These results show that a 1% increase in the proportion of male cancer patients slightly increased the YLL from 3.87% to 4.19%. In very remote areas the YLL increased by 32.05% in 2011 but reduced in 2015 by 22.75%.

However, the cancer burden was significantly increased for those who lived in remote, inner or outer regional areas during the period. In terms of geographical distribution, patients from New South Wales (32%) experienced a significantly higher burden, followed by Victoria (30%) and Queensland (25%), but the changes were stable during this period. In Western Australia and Tasmania, the burden of cancer significantly increased, by 15.72% to 20.80% and 6.29% to 7.90%, respectively. However, the burden of cancer declined for others, including the Northern Territory from 3.77% to 2.43%, and South Australia from 18.65% to 16.65%. Similarly, the magnitude of the cancer burden increased for those in the least advantaged economic resource quintiles.

DISCUSSION

This study aimed to reveal the trends in cancer incidence, related mortality and cancer burden, as well as measure the magnitude of inequality in cancer mortality, incidence and DALYs during the period of 1982 to 2014 in Australia. The study design was an incidence-based on from a health system perspective. Overall incidence and mortality showed an upward trend over the period and the highest average increase in incidence

Table 2 Socioeconomic inequality of cancer incidence and mortality in Australia

	Cancer incidence*				Cancer mortality†				
Index of socioeconomic resources	Number of new cases (N)	Per cent (%)	Average number of new cases	ASIR	Number of deaths (N)	Per cent (%)	Average number of new cases	ASMR	Age-standardised mortality rates/ incidence rates (M/I)
Q_1 (least advantaged)	128 553	21.60	25 711	508.50	52 418	24.12	10 484	190.00	0.374
Q_2	128 472	21.58	25 694	507.70	49 353	22.71	9871	178.70	0.352
Q_3	118 500	19.91	23 700	494.30	43 572	20.05	8714	168.30	0.340
Q_4	108 053	18.15	21 611	487.60	37 358	17.19	7472	158.60	0.325
Q_5 (most advantaged)	118 680	19.94	22 336	488.20	34 648	15.94	6930	142.90	0.293
Total	595 258	100.00	119 303	498.90	217 349	100.00	43 566	168.80	0.338
(Q_1/Q_5)	1.083	1.083	1.151	1.042	1.513	1.513	1.513	1.330	1.276
(Q_1-Q_5)	9873	1.659	3375	20.300	17 770	8.176	3554	47.100	2.320
(Q_1-Q_3)/Q_1	0.078	0.078	0.078	0.028	0.169	0.169	0.169	0.114	4.071
(Q_3-Q_5)/Q_3	−0.002	−0.002	0.058	0.012	0.205	0.205	0.205	0.151	12.583
(Q_1-Q_5)/Q_1	0.077	0.077	0.131	0.040	0.339	0.339	0.339	0.248	6.201
CI (SE)	−0.029 (0.001)				−0.011 (0.002)				
Probability value (p value)	0.001				0.047				

Qi=ith index of economic resources (i=1, 2… 5; higher i represents a quintile with most advantaged economic resources), Q_1-Q_5=least most advantaged economic resources difference (LMD), Q_1/Q_5=least most advantaged economic resources ratio (LMR).
*Incidence reported from 2008 to 2012.
†Mortality rate reported from 2010 to 2014.
ASIR, Age-standardised incidence rates; ASMR, Age-standardised mortality rates; CI, concentration index; SE, SE error.

Table 3 Distribution of cancer cases (2008 to 2012) and cancer-related mortality (2010 to 2014) by cancer site/type and socioeconomic status in Australia

Cancer cases by selected cancer site/type	Index of economic resources					Degree of inequality						
	Q_1	Q_2	Q_3	Q_4	Q_5	Q_1/Q_5	Q_1-Q_5	$(Q_1-Q_3)/Q_1$	$(Q_3-Q_5)/Q_3$	$(Q_1-Q_5)/Q_1$	Concentration index	(LMR of mortality)/(LMR of incidence)
Colorectal	16746	16446	14770	12941	12620	1.327	4126	0.118	0.146	0.246	−0.014	–
Pancreas	3176	2980	2715	2438	2377	1.336	799	0.145	0.124	0.252	−0.015	–
Lung	14142	12310	10488	8556	7196	1.965	6946	0.258	0.314	0.491	−0.065**	–
Melanoma	10998	12155	11681	10721	12170	0.904	−1,172	−0.062	−0.042	−0.107	0.087*	–
Breast	13504	14363	14075	13959	15735	0.858	−2,231	−0.042	−0.118	−0.165	0.104*	–
Cervix	938	894	756	752	688	1.363	250	0.194	0.090	0.267	−0.014	–
Prostate	20657	22087	20793	19057	21636	0.955	−979	−0.007	−0.041	−0.047	0.076**	–
Kidney	3272	3158	2829	2568	2434	1.344	838	0.135	0.140	0.256	−0.014	–
Bladder	2881	2672	2508	2129	2011	1.433	870	0.129	0.198	0.302	−0.002	–
Non-Hodgkin's lymphoma	4653	4659	4564	4482	4654	1.000	-1	0.019	−0.020	0.000	0.001**	–
Unknown primary site	3264	3016	2525	2172	1966	1.660	1298	0.226	0.221	0.398	−0.031	–
Others	34322	33732	30796	28278	28193	1.217	6129	0.103	0.085	0.179	−0.063	–
All cancers combined	128553	128472	118500	108053	111680	1.151	16873	0.078	0.058	0.131	−0.079**	–

Cancer-related mortality by selected cancer site/type	Index of economic resources					Degree of inequality						
	Q1	Q2	Q3	Q4	Q5	Q1/Q5	Q1-Q5	(Q1-Q3)/Q1	(Q3-Q5)/Q3	(Q1-Q5)/Q1	Concentration index)	(LMR of mortality)/(LMR of incidence)
Colorectal	4780	4426	4037	3620	3334	1.434	1446	0.155	0.174	0.303	▶ 0.004	1.081
Pancreas	2906	2709	2509	2247	2105	1.381	801	0.137	0.161	0.276	▶ 0.011	1.034
Lung	10935	9749	8248	6483	5430	2.014	5505	0.246	0.342	0.503	▶ 0.066*	1.025
Melanoma	1638	1664	1543	1367	1367	1.198	271	0.058	0.114	0.165	▶ 0.034**	1.325
Breast	3064	3013	2780	2631	2709	1.131	355	0.093	0.026	0.116	▶ 0.048**	1.318
Cervix	334	267	207	190	136	2.456	198	0.380	0.343	0.593	▶ 0.095*	1.802
Prostate	3714	3676	3234	2651	2568	1.446	1146	0.129	0.206	0.309	▶ 0.007	1.514
Kidney	1109	1037	968	769	707	1.569	402	0.127	0.270	0.362	▶ 0.017	1.167
Bladder	1225	1173	1057	869	827	1.481	398	0.137	0.218	0.325	▶ 0.009	1.033
Non-Hodgkin's lymphoma	1594	1608	1458	1262	1201	1.327	393	0.085	0.176	0.247	▶ 0.014	1.327
Unknown primary site	3414	3181	2587	2228	1937	1.763	1477	0.242	0.251	0.433	▶ 0.043*	1.062
Others	17705	16850	14944	13041	12327	1.436	5378	0.156	0.175	0.304	▶ 0.001	1.180
All cancers combined	52418	49353	43572	37358	34648	1.513	17770	0.169	0.205	0.339	−0.011**	1.315

Qi=ith index of economic resources (i=1, 2… 5; higher i represents a quintile with most advantaged), Q_1-Q_5=least advantaged-most advantaged difference (LMD), Q_1/Q_5=least advantaged-most advantaged ratio (LMR). *p<*0.01*, §p<*0.05*. *p<*0.01*, **p<*0.05*.

Table 4 Burden of cancer (YLL, YLD and DALY/1000) across socioeconomic groups, 2011 to 2015

Associated burden of cancer and annual percentage change	Index of economic resources					Degree of inequality				
	Q_1	Q_2	Q_3	Q_4	Q_5	Q_1-Q_5	Q_1/Q_5	$(Q_1$-$Q_3)/Q_3$	$(Q_3$-$Q_5)/Q_3$	$(Q_1$-$Q_5)/Q_5$
Australian burden of diseases study – 2011										
Fatal burden										
(1) YLL	187.00	175.00	161.00	136.00	125.00	62.00	1.50	0.14	0.22	0.50
(2) ASR	38.10	34.60	32.40	29.50	26.30	11.80	1.45	0.15	0.19	0.45
(3) Rate ratio	1.40	1.30	1.20	1.10	1.00	0.40	1.40	0.14	0.17	0.40
Non-fatal burden										
(4) YLD	10.00	10.00	10.00	10.00	10.00	0.00	1.00	0.00	0.00	0.00
(5) ASR	2.10	2.00	1.90	2.10	2.10	0.00	1.00	0.10	–0.11	0.00
(6) Rate ratio	1.00	1.00	0.90	1.00	1.00	0.00	1.00	0.10	–0.11	0.00
Total burden										
(7) DALY	197.00	185.00	171.00	146.00	135.00	62.00	1.46	0.13	0.21	0.46
(8) ASR	40.20	36.60	34.30	31.60	28.40	11.80	1.42	0.15	0.17	0.42
(9) Rate ratio	1.40	1.30	1.20	1.10	1.00	0.40	1.40	0.14	0.17	0.40
Australian burden of diseases study – 2015										
Fatal burden										
(10) YLL	186.60	184.03	166.63	139.97	124.22	62.38	1.50	0.11	0.34	0.50
(11) ASR	34.00	32.70	30.80	27.70	24.10	9.90	1.41	0.09	0.28	0.41
(12) Rate ratio	1.60	1.40	1.30	1.20	1.10	0.50	1.45	0.19	0.18	0.45
Non-fatal burden										
(13) YLD	12.97	13.31	12.58	12.32	12.98	–0.01	1.00	0.03	–0.03	0.00
(14) ASR	2.30	2.30	2.30	2.40	2.50	–0.20	0.92	0.00	–0.08	–0.08
(15) Rate ratio	1.04	1.00	0.91	1.00	1.00	0.04	1.04	0.13	–0.09	0.04
Total burden										
(16) DALY	199.57	197.34	179.21	152.29	137.20	62.37	1.45	0.10	0.31	0.45
(17) ASR	36.30	35.00	33.10	30.10	26.60	9.70	1.36	0.09	0.24	0.36
(18) Rate ratio	1.40	1.30	1.20	1.10	1.00	0.40	1.40	0.14	0.20	0.40
Annual percentage change										
YLL	–0.04	1.01	0.69	0.58	–0.13	0.12	0.03	–5.23	9.19	0.09
YLD	5.34	5.89	4.70	4.26	5.35	–	–0.02	–	–	–

Continued

Table 4 Continued

Associated burden of cancer and annual percentage change	Index of economic resources					Degree of inequality				
	Q_1	Q_2	Q_3	Q_4	Q_5	Q_1-Q_5	Q_1/Q_5	(Q_1-Q_3)/Q_3	(Q_3-Q_5)/Q_3	(Q_1-Q_5)/Q_5
DALY	0.26	1.30	0.94	0.85	0.32	0.12	−0.07	−4.73	7.83	−0.24
ASR	−2.02	−0.89	−0.71	−0.97	−1.30	−3.84	−0.79	−10.09	7.53	−2.79
Rate ratio	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.40	3.30	0.00

Qi=ith index of economic resources (i=1, 2,…5; higher i represents a quintile with most advantaged), Q_1-Q_5=least advantaged-most advantaged difference (LMD), Q_1/Q_5=least advantaged-most advantaged ratio (LMR).
ASR, age-standardised rates; DALY, disability-adjusted life years; YLD, years lost due to disability;YLL, years of life lost.

was found in the Northern Territory, Australian Capital Territory and Western Australia. Also, the proportion of cancer-related hospitalisation has increased and is dominated by same-day hospitalisations. Further, the survival inequality in terms of LMR of mortality and LMR of incidence was especially high for prostate, cervix, melanoma, non-Hodgkin's lymphoma and breast, suggesting that survival inequality was most pronounced for these cancers. Overall, the fatal burden of cancer exhibited an increasing trend over the period.

The study's findings support a growing body of research evidence that has found the incidence of cancer and cancer-related mortality to be increasing in other country settings.[14 51–54] These increasing trends have been pronounced in the last couple of decades globally.[6 52 53] The WHO[55] and the Sustainable Development Goals[56] have outlined the increasing burden of non-communicable diseases that include cancer, and have promoted initiatives to control and prevent future increases through action plans. Still, the burden of cancer has been growing in Australia over the last decades.[24] Four driving forces have contributed to this: first, increased exposure to risk factors (for example, unbalanced and industrialised-type diets)[57] as well as a high prevalence of obesity[58 59]; second, improved health outcomes (eg, life expectancy)[4] and demographic transition (eg, ageing and growth of population)[5] has reduced death rates compared with other causes of death; third, widespread urbanisation (responsible for the change in lifestyles),[60] exposure to smoking[61] and alcohol consumption[60] are contributing to developing higher cancer risk[60 62] and fourth, overdiagnosis is considered another potential driving force for increasing cancer incidence and related mortality. It is evident from past studies that overdiagnosis has played a significant role in increasing the burden of cancer[63] but that the rising magnitude of cancer burden among Australians may not be entirely explained by overdiagnosis.[64] Therefore, further research that explores the potential risk factors may contribute to a deeper understanding of the reasons behind the increasing burden of cancer in Australia.

This study found that survival inequality was most pronounced for prostate cancers and consistent with previous studies.[65 66] Evidence about underlying causes to explain inequalities in prostate cancer. Some possible explanations can be considered such as factors associated with the tumour (eg, stage at diagnosis, biological characteristics), the patient (comorbidity, health behaviour, psychosocial factors) and the healthcare (treatment, medical expertise, screening).[65–67] Furthermore, the utilisation rate of screening services is lower among prostate cancer patients with disadvantaged socioeconomic status.[68 69] Moreover, patient factors as comorbidity or health behaviour can interact with treatment modalities or disease stage and additionally have a potential impact on inequalities in survival.[70 71] Further, an increased likelihood of surveillance as treatment among patients with severe comorbidity while radical prostatectomy was significantly less likely to be offered.[65 66 69 70] Some studies

Table 6 Association of fatal cancer burden (natural logged of years of life lost) with sex, remoteness, location and socioeconomic resources

	Model 1			Model 2		
Variables	**Coefficient (SE)**	**P value**	**95%**	**Coefficient (SE)**	**P value**	**95%**
Sex						
Male	0.038 (0.034)	0.01	(0.014 to 0.088)	0.041 (0.026)	0.010	(0.011 to 0.091)
Female (ref)	ref	–	–	ref	–	–
Remoteness						
Major cities (ref)	ref	–	–	ref	–	–
Inner regional	0.042 (0.002)	<0.001	(0.014 to 0.080)	0.100 (0.003)	<0.001	(0.025 to 0.174)
Outer regional	0.149 (0.007)	<0.001	(0124 to 0.158)	0.158 (0.001)	<0.001	(0.103 to 0.253)
Remote	0.158 (0.006)	<0.001	(0.113 to 0.246)	0.189 (0.004)	<0.001	(0.149 to 0.343)
Very remote	0.278 (0.009)	<0.001	(0.211 to 0.344)	0.205 (0.002)	<0.001	(0.131 to 0.379)
Location (States)						
Australian Capital Territory (ref)	ref	–	–	ref	–	–
New South Wales	0.282 (0.008)	<0.001	(0.187 to 0.376)	0.278 (0.008)	<0.001	(0.184 to 0.372)
Northern Territory	0.037 (0.009)	0.336	(–0.039 to 0.113)	0.024 (0.004)	0.560	(–0.055 to 0.103)
Queensland	0.234 (0.008)	<0.001	(0.139 to 0.327)	0.223 (0.005)	<0.001	(0.125 to 0.321)
South Australia	0.171 (0.005)	<0.001	(0.084 to 0.258)	0.154 (0.005)	<0.001	(0.065 to 0.243)
Tasmania	0.061 (0.004)	0.167	(–0.026 to 0.148)	0.076 (0.002)	0.070	(–0.007 to 0.158)
Victoria	0.268 (0.005)	<0.001	(0.179 to 0.357)	0.263 (0.005)	<0.001	(0.174 to 0.351)
Western Australia	0.146 (0.009)	<0.003	(0.048 to 0.244)	0.189 (0.004)	<0.001	(0.104 to 0.275)
Index of economic resources						
Q_1 (least advantaged)	0.063 (0.002)	0.032	(0.019 to 0.146)	0.073 (0.004)	0.040	(0.032 to 0.159)
Q_2	0.042 (0.004)	0.331	(–0.043 to 0.128)	0.046 (0.007)	0.320	(–0.045 to 0.138)
Q_3	0.039 (0.001)	0.343	(–0.042 to 0.120)	0.042 (0.004)	0.330	(–0.044 to 0.128)
Q_4	0.011 (0.003)	0.795	(–0.073 to 0.096)	0.010 (0.005)	0.830	(–0.079 to 0.098)
Q_5 (most advantaged)	ref	–	–	ref	–	–
Constant	0.931 (0.004)	<0.001	(0.885 to 0.978)	0.899 (0.008)	<0.001	(0.864 to 0.935)
Family distribution	Gaussian distribution			Gaussian distribution		
Link function	Identity			Identity		
Deviance		25.13		14.85		
Link-test (beta hat)	0.110 (0.018)	<0.001	(0.075 to 0.145)	0.103 (0.008)	<0.001	(0.087 to 0.119)
AIC	1.07			1.02		
BIC	2.92			3.05		

Note: Models 1 and 2 were constructed for 2011 and 2015, respectively; ref=reference group.
AIC, Akaike information criterion; BIC, Bayesian information criterion.

conducted in England,[72] Australia[73] and the USA[74] also revealed that socioeconomically disadvantaged patients have a reduced likelihood of having radical prostatectomy compared with patients with disadvantaged socioeconomic status who utilised more regularly hormone therapy, active surveillance, watchful waiting and partly radiation. There is an ongoing debate regarding the significant role of healthcare management as a contributing factor to inequalities in survival among prostate cancer patients.[67]

The results show that the overall incidence, cancer-related mortality and cancer burden (eg, YLL, YLD and DALYs) were significantly higher among the least advantaged group compared with the most advantaged. It was also found that the least advantaged quintile on average experienced 34% more cancer-related mortality than

their most advantaged counterparts. Similarly, patients in the least advantaged group experienced a significantly higher burden of cancer in terms of YLL (6.50% to 7.57%) compared with the richest (1.11%) from 2011 to 2015. Previous studies have also reported similar inequalities in YLL,[75 76] whereas, a high proportion of patients in the most-deprived groups experienced very high years loss of life. Even though survival rates after cancer diagnosis have improved in recent years,[7] disparities in cancer outcomes between the least-deprived and the most-deprived groups continue to persist. The magnitude of the cancer burden is negatively associated with socioeconomic status.[77–80] For example, adverse health outcomes (eg, worse health status and shorter life expectancy) are disproportionately found in poorer people compared with those in higher quintiles.[77–80] Some reasons that have contributed to the high rate of cancer burden among the poorest groups includes smoking exposure,[51 77] poverty and economic burden,[61 81] increased psychological pressure,[3] lack of health education and awareness[82] and lower access to competent and effective public health interventions.[82] There are several factors which lead to increased breast cancer incidence and cancer-related mortality. These can be classified into patients, tumour and treatment characteristics.[83–85] These characteristics include patient age, ethnicity, tumour type, size, grade, stage, hormone receptor status, type of surgery and the use of adjuvant therapies.[83–85] A recent review study demonstrated that treatment-related factors and socioeconomic disadvantage are also responsible for high cancer burden in Australia.[84]

Moreover, low productivity, loss/reduction of household income and increased expenditure due to illness result in reduced earnings and higher expenditure that further disadvantage the poorest. Growing socioeconomic inequalities of cancer outcomes need the attention of governments, health systems and decision-makers. These initiatives should aim for universal cancer care in all states. A sustained reduction of socioeconomic inequalities, which concerns poverty, gender, education and health, should promote universal equality in health and well-being and further enhance both socioeconomic and human development.

The present study has also identified that the fatal burden of cancer was high in 2011 among patients in very remote areas, but it was reduced by 2015. Similarly, the burden of cancer was high in New South Wales, Victoria and Queensland; however, the magnitude of fatal burden was unchanged during 2011 to 2015. Some previous studies have shown consistent findings, which have confirmed that the proportion of life lost for patients in geographical disadvantaged or low-resource settings had a higher cancer burden than their more advantaged counterparts.[75 76] Socioeconomic inequalities in terms of poorer survival for geographically isolated patients was observed in cancer types in Australia including breast and colorectal cancer.[86] Several issues might be associated with a high burden of cancer among patients in regional and remote Australia, including a lack of appropriate skills among health professionals and a lack of adequate resources being available in remote and smaller cities.[15 33 87] A recent study conducted in regional Australia identified that there was a paucity of medical professionals with expertise and appropriate cancer training in regional areas.[68] The study also confirmed that a lack of communication and coordination persisted between different medical professionals (such as oncologists and GPs) and across geographical locations (major vs regional centres).

Difficulty in service accessibility and availability of appropriate cancer care services is faced by residents of rural, remote communities in Australia.[87] However, only 30% of the population lives outside the major cities.[88] The federal government has committed to improving the cancer infrastructure by building a network of new and enhanced regional cancer centres in regional Australia.[89] Furthermore, innovative cancer care models, including mobile clinics incorporating video conference and tele-oncology, have been introduced in order to address the challenges of distance. Advanced technology-based services such as tele-oncology have been implemented in Western Australia and North Queensland, allowing regional cancer patients to use the latest treatments including specialist consultations and chemotherapy treatments.[90 91] These models have also been implemented in the USA and Canada to ensure maximum access to services among people in limited resources settings, with high levels of satisfaction and acceptance of services.[90–94]

This study contributes to the existing literature by providing first-hand evidence on the trends of incidence, mortality and burden of cancer, using Australian nationally representative population-based data. This study has used large national level data sets covering all states over the past 33 years. Due to paucity of survival data, this study has not captured in details inequalities regarding the cancer survivorship. However, there is a limited understanding of what is driving these changes of cancer outcomes reported here which may reflect random variation or changes in unknown risk factors, and therefore highlight the need for more research into the aetiology of cancer.

CONCLUSIONS

The overall burden of cancer is substantial in Australia across all socioeconomic strata and geographical regions. Compared with socioeconomically advantaged people, disadvantaged people had a substantially higher risk of cancer incidence and cancer-related mortality. Those living in remote areas also bear a higher burden than those in urban areas who are closer to prevention and treatment services. The findings of this study can inform efforts by healthcare policymakers and those involved in healthcare systems to improve cancer survival in Australia. This work also suggests that the provision of universal cancer care can reduce the burden by ensuring curable

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and preventive cancer care services are accessible for all people regardless of socioeconomic status or location.

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Correction: ***Emerging cancer incidence, mortality, hospitalisation and associated burden among Australian cancer patients, 1982 – 2014: an incidence-based approach in terms of trends, determinants and inequality***

Mahumud RA, Alam K, Dunn J, *et al*. Emerging cancer incidence, mortality, hospitalisation and associated burden among Australian cancer patients, 1982– 2014: an incidence-based approach in terms of trends, determinants and inequality. *BMJ Open* 2019;9:e031874. doi: 10.1136/bmjopen-2019-031874

This article was previously published with an error in figures. The correct figures are below:

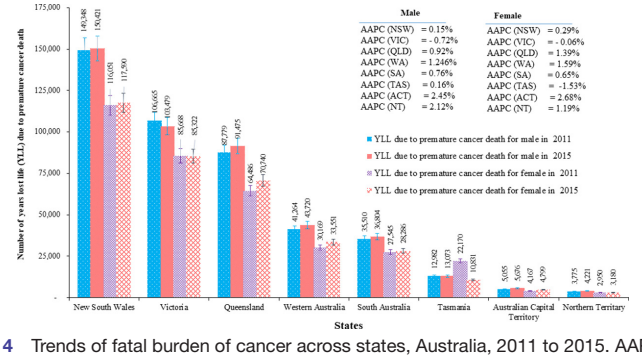

Figure 4 Trends of fatal burden of cancer across states, Australia, 2011 to 2015. AAPC, average annual percentage change; act, Australian Capital Territory; NSW, New South Wales; nt, Northern Territory; QLD, Queensland; SA, South Australia; tas, Tasmania; VIC, Victoria; WA, Western Australia.

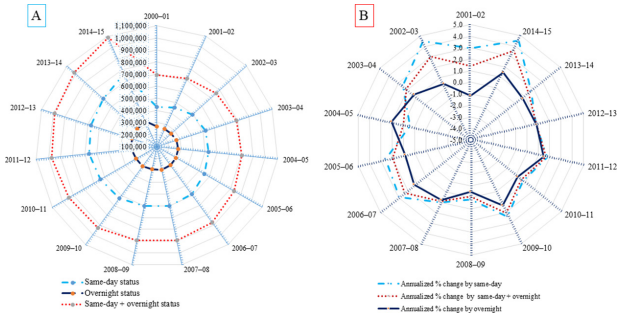

Figure 5 Distribution of cancer-related hospitalisations by same-day and overnight status in Australia, 2000 to 2015.

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2.2 Study 2

Cancer burden: Long-term health status burden and consequences

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The *first study* of this thesis explored the understanding challenges of long-term national level cancer outcomes in Australia. Study 2 examined the long-term health status burden and consequences over an extended period.

Article II: The impact of lifestyle risk factors, life satisfaction and chronic comorbid conditions on influencing in longitudinal health status burden among Australian cancer patients, 2013-2017

The purpose of *Study 2* was to examine longitudinal measures in health status burden among cancer patients and its associated predictors. The findings of the study showed that approximately 36% of cancer survivors had an initial high health status burden in 2013, while it had declined significantly (21%) by 2017. This was evidenced in significant improvements in body pain, social functioning, and mental health measures. Adequate levels of sleep, physical activity, social support, and higher economic status were significantly associated with improving health status. Factors that negatively influenced changes in health status burden included being unemployed, Indigenous, uninsured, living in a regional location, and having comorbid conditions. The *Study 2* concludes that these findings shed light on which benefits attached to the health care system might be more valuable to cancer survivors. There is growing recognition of the importance of patient-focused outcomes in cancer care. The quality of a person's life and the personal preferences and values of that person guide their health care, and thus should have a high priority in policy discussions.

2.2.1 Article II

The impact of lifestyle risk factors, life satisfaction and chronic comorbid conditions on influencing in longitudinal health status burden among Australian cancer patients, 2013-2017 (*under review*: *BMJ Open***)**

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Abstract

Objective: Cancer is one of the most public health concerns and the second leading cause of death worldwide. A cancer diagnosis signifies a negative effect on both short-term and long-term changes in their health status. The main objective of this study was to examine longitudinal measures in health status burden among cancer patients and its associated predictors.

Settings: The study was conducted in Australia.

Study design: A mixed longitudinal study design was used.

Methods: The longitudinal effect was captured using generalized linear mixed model (GLMM) which estimated changes in health status burden influenced by socio-demographic, lifestyle, life conditions and location specific variables.

Results: Approximately 36% of cancer survivors had an initial high health status burden in 2013, while it had declined significantly (21%) by 2017. The health status outcomes improved over the period (59.56 points to 65.06 points; $p = 0.05$). This was evidenced in significant improvements in body pain; social functioning; and mental health measures. Adequate levels of sleep, physical activity, social support, and higher economic status were significantly associated with improving health status. Factors that negatively influenced changes in health status burden included being unemployed, Indigenous, uninsured, living in a regional location, and having comorbid conditions.

Conclusions: The study findings shed light on which benefits attached to the health care system might be more valuable to cancer survivors. There is growing recognition of the importance of patient-focused outcomes in cancer care. The quality of a person's life and the personal preferences and values of that person guide their health care, and thus should have a high priority in policy discussions.

Keywords

Cancer survivors, Comorbid conditions, Longitudinal, Health status burden, Australia.

Strengths and limitations of this study

- This study examined longitudinal measures in health status burden among cancer patients and its associated predictors in the Australian context
- This study included the prospective design of long term follow up, and the application of well-validated and reliable longitudinal wave measures of the impacts of cancer diagnosis on the health status burden.
- This study considered the overall health status of cancer survivors, which might vary in terms of cancer stages and types of cancer.
- The study findings were based on self-reported information that might have been impacted by respondents' prejudice (e.g., silence and over-response), or due to problems in understanding and interpretation.

Background

Cancer is one of the most public health concerns and the second leading cause of death worldwide [1]; an estimated 9.6 million patients die from cancer each year. In Australia, it is also an alarming issue with the health system dealing with 483 new cases per 100,000 people in 2019, while on average 136 people will die from cancer each day [2]. Cancer accounts for 19% of the total burden of disease, followed by 15% from cardiovascular diseases, and 12% from mental illness [3]. Increasing innovations in medical technology have played a significant role in earlier diagnoses and improved courses of treatment of several cancers have resulted in many people diagnosed with cancer having improved chances of surviving over the past few decades [4,5]. Globally, five-year survival rates have increased significantly from 50% in 1990 to almost 70% in 2015 [2]. The survival rates vary across cancer type or sites in terms of the risk of developing and dying from cancer. Survivors face numerous physical, mental, social, spiritual and economic challenges as a result of their diagnosis, during their course of treatment, and for the remaining years of their lives. In addition, a cancer diagnosis signifies a negative effect on both short-term and long-term changes in their health status, including their health-related quality of life (*HRQoL*).

Many of these problems could be ameliorated through public health initiatives, both through the prevention of secondary diseases or recurrence of cancer, and by improving the quality of life for each survivor. The quality of life for cancer

survivors is significant because of increasing and relatively high survival rates and extended life after diagnosis. The majority of cancer survivors living longer will be at a higher risk of long-term and late onset effects, as well as developing new cancers [5]. Moreover, cancer survivors suffer treatment-related side effects, leading to a substantial burden, impairing health status, reducing their independent physical capability, and decreasing productivity [6], which together leads to a decrease in a victim's socioeconomic position [4]. Cancer survivors experience may challenge to their health status.

Studying health status among cancer survivors is warranted. Globally, health status has been attracting considerable attention. Even with advanced treatment of side effects, cancer survivors undergo experiences that often reduce their capacity to conduct their usual activities, which in turn may affect their overall health status. Measuring health status has been integrated into the examination of treatment impacts on quality of life [7]. Understanding the quality of life outcomes of cancer survivors is important in examining their adverse post-treatment outcomes and can help to improve their health status [8]. The quality of life includes different dimensions of health status, such as self-reported functioning and well-being in the physical, psychological, and social domains. The concept of quality of life provides a comprehensive measure that includes mental, physical and social functioning capacity. In recent decades, quality of life assessments has become routine examinations used to evaluate health status in terms of treatment outcomes among cancer survivors [7–9]. Despite this, very little attention has been paid to measuring longitudinal quality of life in diagnosed cancer survivors during the oncology follow-up period.

A range of studies have previously quantified health status among cancer survivors in terms of treatment or surgical outcomes, and access to palliative care in different national settings [9–14]. The health status of cancer survivors' issues is multifactorial and complex, and it is not always effortlessly addressed by medical professionals or during routine oncology follow-ups. The health status of cancer survivors can be adversely affected by pain [15], compromised nutritional status [16], and eating problems [17]. The ongoing evidence suggests that modifying or avoiding risk factors, such as alcohol consumption and an unhealthy diet with low fruit and vegetable intake, can significantly reduce the burden of cancer [1]. Moreover,

engaging in physical activities can lead to improved health status outcomes among cancer survivors [15].

Similarly, cancer survivors who engage in less sedentary behaviour enjoy better quality of life, and this can also significantly contribute to reducing the risk of chronic comorbid conditions [18]. Furthermore, the comorbid condition of cancer survivors is an important parameter to predict a worse health status [19,20]. The patterns of cancer survivors' life satisfaction factors (e.g., satisfaction with financial or social supports) are a crucial predictor of higher health status scores [10,21], but these satisfaction trajectories may vary over time. In terms of location, cancer survivors who live in remote areas like regional Australia experience a worse quality of life than those living in more urban settings [11,16]. The primary intention of these studies was to examine the impact of treatment or surgical outcomes on quality of life in terms of a cross-sectional, clinical or randomised control trial, considering a limited range of variables. The majority of studies pay little attention to examining the long-term impact of health status for cancer survivors' over time. Therefore, it is significant for routine oncology follow-ups to explore how cancer survivors' characteristics impact on health status outcomes, by examining the same individuals over an extended period.

This study will measure the mixed longitudinal nature of health status outcomes. More specifically, the study proposes to develop a better understanding of the health burden in terms of quality of life, as well as its impact over longer periods. This study complements and contributes to this strand of ongoing cancer research to increase awareness and improve public health practice among sufferers and survivors, and to measure impact. Further, the findings could contribute to policy discussions around designing appropriate interventions or the provision of quality healthcare services and resources for ongoing surveillance of people living with, through and beyond cancer, and to determine what kinds of support survivors need.

The point of departure of this study was to use patients' self-reporting of their health status to examine the longitudinal nature of cancer patients' health status and to determine the factors that predict their health status over the period. This will be achieved by using a special data set from the Household, Income and Labour

Dynamics in Australia (*HILDA*) survey. To achieve the research objective, the following two research questions (*RQ*) were posited:

RQ-1: What is the longitudinal nature of health outcomes and the extent of health status burden among cancer patients in Australia?

RQ-2: How does life style factors reflect on health status burden of cancer survivors in Australia?

Material and methods

Study design and perspective

Data were extracted from the Household, Income and Labour Dynamics in Australia (*HILDA*) survey which is a nationally representative longitudinal study of Australian households. It commenced in 2001 and produces longitudinal data on the lives of Australian residents. A wide range of information on relationships, child care, employment, income, health and wellbeing is covered. Data were collected from selected household members aged 15 or over through face-to-face interviews, using quantitative structural instruments and then re-interviews with the same people in subsequent years. The study participants were derived from *HILDA* wave-13 in 2013 (n = 517) and wave-17 in 2017 (n = 576). However, the present study design was considered a mixed longitudinal perspective for two reasons: a limited number of cancer patients participated in the HILDA survey; the mortality rate was also high among cancer patients, and the temporal changes or treatment effects among the study participants were captured. A mixed-longitudinal study design in which several cohorts are followed for a shorter period are compared by their precision, potential for bias due to age, time and cohort effects, and feasibility. In addition, a mixed longitudinal study has two advantages over longitudinal studies: isolation of time and age effects and shorter completion time.

The mixed longitudinal study perspective was underpinned by a stress-coping theory in order to determine if it could predict *HRQoL* of cancer survivors over an extended period. The analytical framework of the stress-coping theory was designed by Lazarus and colleagues [22,23] to investigate which antecedent factors may be aligned with better quality of life outcomes. They investigated individuals who faced the burden of life-threatening cancer and examined the magnitude of the cancer

burden associated with its initial appraisal as well as their ability to manage the secondary occurrence appraisal. In terms of secondary appraisal, individuals reconsidered their health status based on the magnitude of the burden (as either more or less). The theory of stress-coping is that the burden extended over an extended period adversely affects health status, including health status outcomes [23]. To examine the longitudinal effects of the model, it is hypothesised that several antecedent variables (e.g., individual characteristics, social factors, and disease-related factors), measured at the symptom-level might predict outcome factors (appraisal of disease with comorbidities, course of treatment, caregiving, life condition, uncertainty). Moreover, the combination of factors (e.g., antecedent and outcomes) was assumed to predict patients' health status outcomes.

Measuring health status burden of cancer patients

The quality of life scores was measured using the medical outcomes study short-form (*SF-36*) [24]. The *SF-36* is one of the most common and widely used tools when it comes to self-completion measures of quality of life, which is widely used to assess the burden of disease in the context of different country settings [25]. The *SF-36* was designed to examine an individual's health status across eight domains including physical functioning, role-physical, body pain, general health, vitality, social functioning, role-emotional, and mental health. It has psychometric properties to enable profiling of physical functional health and well-being and to quantify disease burden across eight domains [26]. Considering these dimensions, the total score on each *SF-36* subscale ranges between 0 and 100, labelling 'worst imaginable health' and 'best imaginable health state', respectively. It is signified that the higher scores represent better health outcomes. Health status burden was measured based on total quality of life scores and levels were: high burden if *SF-36* score was less than 50 points; moderate burden if *SF-36* score was greater than or equal to 50 but less than 90; and no burden if *SF-36* score was greater than or equal to 90 [27].

Variable selection

Several demographic, socioeconomic and health and lifestyle-related variables were used as predictors of health status outcomes. The domains of these study variables were selected based on stress-coping theory and the literature. The socio-demographic related variables included were: gender, age, educational background,

employment status and marital status. Ethnic background was defined as Aboriginal or non-Aboriginal. Lifestyle factors included hours of sleep per night and physical activities status. Life conditions-related variables, such as satisfaction with household members, employment, financial situation and social supports, were also considered as potential predictors. The level of satisfaction-related variables ranged from 0 (totally dissatisfied) to 10 (totally satisfied). Private insurance coverage of participants was defined as dichotomous ('insured' if present or 'uninsured' otherwise). Treatment status was defined as 'with medication' or 'without medication'. The comorbid condition was dichotomous as 'yes' if the participant had arthritis or osteoporosis, chronic bronchitis or emphysema, diabetes, heart or coronary disease, depression or anxiety, high blood pressure or hypertension, obesity, or any other circulatory condition or other mental illness, or 'no' otherwise. This study covered each comorbid condition in the analyses, rather than using a comorbidity index [28] because such indices were designed to predict survival outcomes and include diagnoses associated with morbidity (e.g., arthritis). Furthermore, severity information, which is important for measuring a comorbidity index, was not captured in the survey data.

Location was defined according to the accessibility to services and the Remoteness Index of Australia [29]. Location was classified into five groups: major cities, inner regional, outer regional, and remote or very remote. The index of relative socio-economic disadvantage (*IRSD*) was considered to measure socioeconomic status (*SES*). The *IRSD* was constructed using factors such as the percentage of occupants in each statistical local area (*SLA*) in terms of income and their educational level, and whether they were in unskilled occupations, or unemployed [30]. This was a geographical area-based estimate of socioeconomic status whereby communities were categorised from economically disadvantaged to wealthy. The cut-off values for each of the quintiles were as follows: Q_1 ($IRSD \leq 927.0$), Q_2 ($927.0 > IRSD \leq 965.8$), Q_3 ($965.8 > IRSD \leq 1001.8$), Q_4 ($1001.8 > IRSD \leq 1056.0$), or Q_5 ($IRSD > 1056.0$) [30]. Each quintile represents an increasing advantage that corresponds to geographical settings, covering the 20% of the population in the lowest socio-economic position (Q_1, most disadvantaged), while the fifth quintile (Q_5) refers to the 20% of the population occupying the highest socioeconomic position.

Estimation strategies

The descriptive analyses quantify the distribution of participants reporting health status scores over the study period. A paired t-test was performed to compare health status scores among cancer survivors, since the mean score of health status outcome was continuous and quantitative in nature. Data were gathered from the participants across two successive points in time; these repeated data were correlated over the period. Generalized linear mixed model (*GLMM*) was performed to find the potential predictors that influenced in health status burden of cancer patients. The *GLMM* model produces more efficient and unbiased regression estimates when examining quantitative nature continuous outcome variable in longitudinal study design. The *GLMM* model extends the generalized linear mixed model to accommodate correlated data. Longitudinal study design has the purpose of explaining the marginal expectations of the outcome as a function of the potential predictors. The *GLMM* model provided a framework for the analyses of quantitative outcomes (e.g., continuous outcomes), but relaxes several assumptions of traditional regression models. It has however been assumed that the outcome variable (health status scores) are linearly connected to the predictors. In addition, the model was tested for sensitivity with the robust standard error to ultimately identify a parsimonious model. In this study, two-tailed probability values of <0.05 were considered as the statistically significant level. Data management and all statistical analyses were undertaken using Stata/SE 13.0 (StataCorp, College Station, TX, USA).

Patient and public involvement:

Patient and public were not involved in the design or planning of this study.

Results

Background characteristics of study participants

The distribution of demographic characteristics, the sample consisted of 54% males with an average age of 63 (± 17) years in 2013, while this was 56% in 2017. Most were aged over 46 years (84%) at diagnosis and 86% in the period of 2017. Approximately half of the participants had completed tertiary or technical education, and 58% of patients were married. Furthermore, 33% of cancer patients reported being employed in 2013, but the proportion of employed wherein 36% in 2017. Two-thirds of patients exhibited an adequate sleep duration (≥ 6 hours/night) while 50% of patients undertook moderate or high-level physical activities each week. Among the sample, 60% of cancer survivors had health insurance coverage. Regarding the life satisfaction score, the average satisfaction scores (standard deviation) were 8.10 points (±1.87), 3.32 points (± 3.89), 6.55 points (± 2.48) and 7.76 points (± 1.98), respectively, for household member, employment, financial situation and social supports. In terms of comorbid conditions at diagnosis: arthritis or osteoporosis (42%), high blood pressure/hypertension (37%), obesity (25%), depression or anxiety (19%), asthma (16%), heart/coronary disease (16%), diabetes (14%), or chronic bronchitis or emphysema (7%) in 2013. Approximately 74% of cancer survivors had utilised cancer-related medication at diagnosis which had increased to 70% in 2017. Nearly 65% of patients lived in major cities in 2013, followed by regional locations (30%).

Table 1. Background characteristics of cancer survivors

Characteristics	Cancer survivors in 2013 (n = 517)		Cancer patients in wave-17 (n = 576)	
	Percentage (%)	**95% CI**	**Percentage (%)**	**95% CI**
Sex				
Male	53.90	(49.64 , 58.24)	56.08	(51.98 , 60.09)
Female	46.00	(41.76 , 50.36)	43.92	(39.91 , 48.02)
Age				
<25 years	3.20	(02.05 , 05.23)	02.95	(01.83 , 04.70)
25-45 years	12.38	(09.80 , 15.52)	10.76	(08.48 , 13.58)
46-65 years	36.94	(32.88 , 41.21)	36.46	(32.61 , 40.48)
>65 years	47.39	(43.10 , 51.72)	49.83	(45.74 , 53.91)
Educational attainment				
Year 11 or below	36.56	(32.50 , 40.81)	34.55	(30.76 , 38.54)
Year 12	07.16	(05.22 , 09.73)	07.99	(06.03 , 10.51)
Trade/certificate/diploma	41.97	(37.77 , 46.29)	40.28	(36.33 , 44.35)
Tertiary	14.31	(11.54 , 17.62)	17.19	(14.31 , 20.50)
Employment status				
Employed	33.27	(29.33 , 37.46)	35.94	(32.11 , 39.95)
Unemployed	66.73	(62.54 , 70.67)	64.06	(60.05 , 67.89)
Marital status				
Single	12.19	(09.63 , 15.31)	12.67	(10.19 , 15.66)
Married	58.61	(54.29 , 62.79)	57.12	(53.03 , 61.15)
Others (separated, divorced or widowed)	29.21	(25.43 , 33.29)	30.21	(26.58 , 30.09)
Ethnic status				
Aboriginal	98.07	(96.44 , 98.96)	98.09	(95.58 , 98.94)
Non aboriginal	01.93	(01.04 , 03.56)	01.91	(01.05 , 03.42)
Hours of sleep per week				
<6 hours	23.60	(20.12 , 27.46)	25.35	(21.95 , 29.07)
≥6 hours	76.40	(72.54 , 79.88)	74.65	(70.93 , 78.05)
Physical activity status				
Low	43.33	(39.10 , 47.65)	47.22	(43.16 , 51.32)
Moderate	32.69	(28.77 , 36.87)	30.73	(27.08 , 34.63)
High	23.98	(20.49 , 27.87)	22.05	(18.84 , 25.63)
Health insurance coverage (= insured)	55.51	(51.18 , 59.76)	56.60	(52.50 , 60.60)
Life conditions, mean scores (SD)				
Satisfaction with household members	8.10 (01.87)	(07.94 , 08.26)	8.08 (1.92)	(07.92 , 08.24)
Satisfaction overall employment	3.32 (03.89)	(02.99 , 03.66)	3.09 (3.87)	(02.78 , 03.41)
Satisfaction financial situation	6.55 (02.48)	(06.34 , 06.77)	6.75 (2.38)	(06.55 , 06.94)
Satisfaction with social supports	7.76 (01.98)	(07.59 , 07.93)	7.76 (1.79)	(07.62 , 07.91)
Diagnosed with co-morbidities				
Arthritis or osteoporosis (= yes)	41.97	(37.77 , 46.29)	38.02	(34.13 , 42.07)
Asthma (= yes)	15.86	(12.95 , 19.28)	14.24	(11.61 , 17.34)
Chronic bronchitis or emphysema (= yes)	07.16	(05.22 , 09.73)	06.08	(04.39 , 08.35)
Diabetes (= yes)	14.12	(11.37 , 17.41)	13.89	(11.29 , 16.97)
Heart /Coronary disease (= yes)	15.67	(12.77 , 19.07)	16.67	(13.83 , 19.95)
Depression or anxiety (=yes)	19.34	(16.15 , 22.99)	23.09	(19.82 , 26.72)
Other mental illness(= yes)	02.32	(01.32 , 04.05)	02.96	(1.84 , 04.70)
High blood pressure/hypertension (= yes)	36.75	(32.69 , 41.01)	37.15	(33.29 , 41.19)
Obesity (= yes)	24.95	(21.39 , 28.88)	26.56	(23.11 , 30.33)
Any other circulatory condition (= yes)	10.06	(07.74 , 12.98)	07.64	(05.73 , 10.19)
Treatment status for diagnosed cancer				
With medication	73.96	(70.21 , 77.39)	70.21	(70.21 , 77.39)
Without medication	26.04	(22.61 , 29.79)	22.61	(22.61 , 29.79)
Location				
Major cities	64.80	(60.56 , 68.81)	59.90	(55.82 , 63.84)
Inner regional	22.63	(19.22 , 26.45)	28.30	(24.76 , 32.13)
Outer regional	11.41	(08.94 , 14.46)	09.38	(07.24 , 12.05)
Remote or very remote	01.16	(0.520 , 02.57)	02.43	(01.44 , 04.07)

Table 1. (Continued)

Characteristics	Cancer survivors in 2013 (n = 517)		Cancer patients in wave-17 (n = 576)	
	Percentage (%)	95% CI	Percentage (%)	95% CI
Socioeconomic status				
Q_1 (lowest 20%) (ref)	22.24	(18.85 , 26.05)	18.06	(15.12 , 21.42)
Q_2	23.02	(19.58 , 26.86)	22.92	(19.66 , 26.54)
Q_3	14.89	(12.07 , 18.24)	17.71	(14.79 , 21.05)
Q_4	20.50	(17.23 , 24.21)	20.14	(17.05 , 23.62)
Q_5 (highest 20%)	19.34	(16.15 , 22.99)	21.18	(18.03 , 24.72)

Longitudinal nature of health status burden among cancer patients

Table 2 shows the distribution of health status scores across cancer survivor characteristics and the changes over the period. There was a significant improvement in health status scores in males (59.85 points to 66.57 points; $p<0.001$); older patients (54.82 points to 62.76 points; $p<0.001$); the unemployed (54.68 points to 62.69 points; $p<0.001$); those of non-Aboriginal heritage (59.61 points to 65.30 points; $p<0.001$); those with adequate sleeping hours (61.35 points to 75.89 points; $p<0.001$); the uninsured (51.64 points to 60.66 points; $p<0.01$); those with an adequate level of physical activity (69.94 points to 75.17 points; $p<0.001$); patients in the medication group (53.48 points to 62.43 points; $p<0.01$); and for those who lived in major cities (59.88 points to 66.36 points; $p<0.01$).

Table 2. Distribution of health status scores among cancer patients

Characteristics	Cancer patients in wave-13 (2013) (Mean ± SD)	Cancer patients in wave-17 (2017) (Mean ± SD)	Mean difference over time (95% CI)[1]
Sex			
Male	59.85 ± 24.90	66.57 ± 16.34	6.72*** (1.24 , 12.20)
Female	58.21 ± 24.99	62.70 ± 17.33	4.49 (-2.34 , 11.32)
Age			
<25 years	60.82 ± 26.97	62.95 ± 17.78	2.13 (-24.82 , 29.08)
25-45 years	59.53 ± 26.60	69.05 ± 17.50	9.52 (-11.08 , 30.12)
46-65 years	64.27 ± 23.76	68.99 ± 17.78	4.72 (-2.50 , 11.94)
>65 years	54.82 ± 24.60	62.76 ± 15.95	7.94*** (2.43 , 13.45)
Educational attainment			
Year 11 or below	51.58 ± 24.62	62.17 ± 16.31	10.59*** (3.90 , 17.28)
Year 12	64.15 ± 24.03	66.70 ± 19.21	2.55 (-14.07 , 19.17)
Trade/certificate/diploma	62.65 ± 24.25	68.08 ± 16.30	5.43 (-1.37 , 12.23)
Tertiary	65.35 ± 23.94	64.72 ± 17.83	-0.63 (-11.18 , 9.92)
Employment status			
Employed	67.95 ± 22.99	71.54 ± 14.17	3.59 (-3.89 , 11.07)
Unemployed	54.68 ± 24.72	62.69 ± 17.10	8.01*** (3.02 , 13.00)
Marital status			
Single	51.69 ± 26.63	62.74 ± 15.08	11.05 (-2.39 , 24.49)
Married	62.64 ± 23.92	67.10 ± 16.87	4.46 (-0.80 , 9.72)
Others	55.07 ± 25.07	61.37 ± 16.90	6.30 (-1.98 , 14.58)
Ethnic status (= non aboriginal)	59.61 ± 24.74	65.30 ± 16.72	5.69*** (1.43 , 9.95)
Hours of sleep per week			
<6 hours	51.80 ± 24.55	62.28 ± 16.94	10.48** (1.62 , 19.34)
≥6 hours	61.35 ± 24.65	65.89 ± 16.72	4.54* (2.27 , 9.35)

(Continued)

Table 2. (Continued)

Characteristics	Cancer patients in wave-13 (2013) (Mean ± SD)	Cancer patients in wave-17 (2017) (Mean ± SD)	Mean difference over time (95% CI)[1]
Physical activity status			
Low	49.78 ± 24.66	59.56 ± 15.72	9.78*** (3.66 , 15.90)
Moderate	63.48 ± 22.14	66.55 ± 16.93	3.07 (-3.86 , 10.00)
High	69.94 ± 23.09	75.17 ± 13.88	5.23 (-3.21 , 13.67)
Smoking exposure			
No	60.05 ± 25.01	65.86 ± 16.72	5.81** (1.28 , 10.34)
Yes	52.57 ± 23.55	58.50 ± 16.36	5.93 (-6.48 , 18.34)
Health insurance coverage			
Insured	65.07 ± 23.31	67.16 ± 17.32	2.09 (-2.90 , 7.08)
Uninsured	51.64 ± 24.93	60.66 ± 14.81	9.02** (1.67 , 16.37)
Diagnosed with co-morbidities			
Arthritis or osteoporosis (= yes)	51.50 ± 22.05	61.04 ± 15.43	9.54*** (3.57 , 15.51)
Asthma (= yes)	49.03 ± 23.43	54.16 ± 15.77	5.13 (-5.60 , 15.86)
Chronic bronchitis or emphysema (= yes)	38.80 ± 21.03	57.34 ± 11.43	18.54* (3.23 , 40.31)
Diabetes (= yes)	48.64 ± 23.23	59.45 ± 13.94	10.81*** (1.64 , 19.98)
Heart /Coronary disease (= yes)	47.84 ± 22.42	59.73 ± 16.73	11.89*** (2.71 , 21.07)
Depression or anxiety (= yes)	42.48 ± 21.69	50.36 ± 12.37	7.88 (-1.83 , 17.59)
Other mental illness (= yes)	25.31 ± 08.16	45.26 ± 7.15	19.95*** (8.78 , 31.12)
High blood pressure/hypertension (= yes)	55.87 ± 22.68	62.12 ± 15.18	6.25** (0.48 , 12.02)
Obesity (= yes)	60.06 ± 21.76	59.30 ± 15.67	-0.76 (-7.86 , 6.34)
Any other circulatory condition (= yes)	43.02 ± 18.28	56.31 ± 19.64	13.29** (2.12 , 24.46)
Treatment status for diagnosed cancer			
With medication	53.48 ± 23.70	62.43 ± 16.18	8.95*** (4.45 , 13.45)
Without medication	72.69 ± 22.56	78.14 ± 13.48	5.45 (-3.73 , 14.63)
Location			
Major cities	59.88 ± 25.21	66.36 ± 17.29	6.48** (1.14 , 11.82)
Inner regional	60.42 ± 23.72	63.21 ± 14.98	2.79 (-5.60 , 11.18)
Outer regional	52.15 ± 25.11	62.19 ± 20.09	10.04 (-5.36 , 25.44)
Remote or very remote	57.50 ± 26.05	58.20 ± 03.72	0.70 (-30.14 , 31.54)
Socioeconomic status			
Q_1 (lowest 20%) (ref)	49.46 ± 23.98	58.53 ± 17.08	9.07* (-0.15 , 18.29)
Q_2	57.71 ± 24.52	64.62 ± 17.55	6.91 (-2.24 , 16.06)
Q_3	59.89 ± 25.26	66.62 ± 16.81	6.73 (-4.01 , 17.47)
Q_4	59.88 ± 24.91	62.98 ± 14.40	3.10 (-6.80 , 13.00)
Q_5 (highest 20%)	70.38 ± 21.78	71.58 ± 15.88	1.20 (-6.74 , 9.14)

[1]Two sample t-test performed, ***, ** and * denotes significant at 0.1%, 1% and 5% risk level respectively and Qi = ith wealth quintile (i =1, 2. . . 5; higher i represents a quintile with higher wealth), SD = standard deviation, CI = confidence interval.

Although overall cancer patient's health status outcomes improved during the period across health states, a significant improvement was observed in terms of body pain (54.93 points to 60.26 points; $p<0.05$); social functioning (67.11 points to 73.46 points; $p = 0.027$); and mental health (67.41 points to 72.23 points; $p = 0.028$). Furthermore, a monotonic decline in health burden was most pronounced for the SF-36 scales. There was a significant reduction of 'high health burden' among cancer survivors (36% to 21%; $p<0.01$) (Figure 1). A significant reduction was also observed in physical functioning (34% to 26%; $p<0.05$); role-physical (50% to 9%; $p<0.001$); social functioning (27% to 17%; $p = 0.04$); role-emotional (36% to 9%; $p <0.001$); and mental health (21% to 9%; $p = 0.002$).

Factors influencing health status scores among cancer survivors

Several predictors had a significant and independent impact on health status (Table 3). A block of socio-demographic, ethnicity, and lifestyle variables were included in model-1. Unemployed (β = -6.28 points; *p<0.001*) and Indigenous (β = -14.81 points; *p<0.001*) cancer survivors had significantly worse health status outcomes. However, cancer survivors who were married (β = 4.66 points; *p<0.001*); were highly educated (β = 10.29 points; *p<0.001*); had adequate sleep (β = 5.41 points; *p<0.001*); and who maintained a moderate (β = 9.33 points; *p<0.001*) or adequate (β = 15.65 points; *p<0.001*) level of physical activity had higher health status. An additional set of control predictors to account for a range of different life conditions were introduced in model-2. Cancer patients' satisfaction related to their financial situation (β = 1.98 points; *p<0.001*); and level of social support (β = 1.10 points; *p<0.001*) were also decisively associated with higher health status scores. Conversely, cancer survivors without health insurance coverage (β = -4.31 points; *p<0.001*); and those who were on prescription medication (β = -9.55 points; *p<0.001*) had significantly worse health status scores compared to their counterparts. Comorbid conditions were examined in model-3. The majority of the reported comorbid condition survivors had a significantly lower quality of life compared to those without exposure to conditions including arthritis or osteoporosis (β =-3.84 points; *p<0.001*); chronic bronchitis or emphysema (β =-9.94 points; *p<0.001*); heart or coronary disease (β = -4.26 points; *p<0.01*); depression or anxiety (β = -8.21 points; *p<0.001*); or another mental illness (β = -4.26 points; *p<0.01*). Finally, location and socioeconomic position-related variables were introduced in model-4. Patients who lived in regional locations (β = -7.17 points; *p<0.001*) had a significantly worse health status, while patients belonging to the richest households (β = 1.49 points; *p<0.01*) had a better health status compared with their lowest quintile counterparts.

Figure 1. Distribution of health burden among patients with cancer over 4-year follow-up period (2013 to 2017)

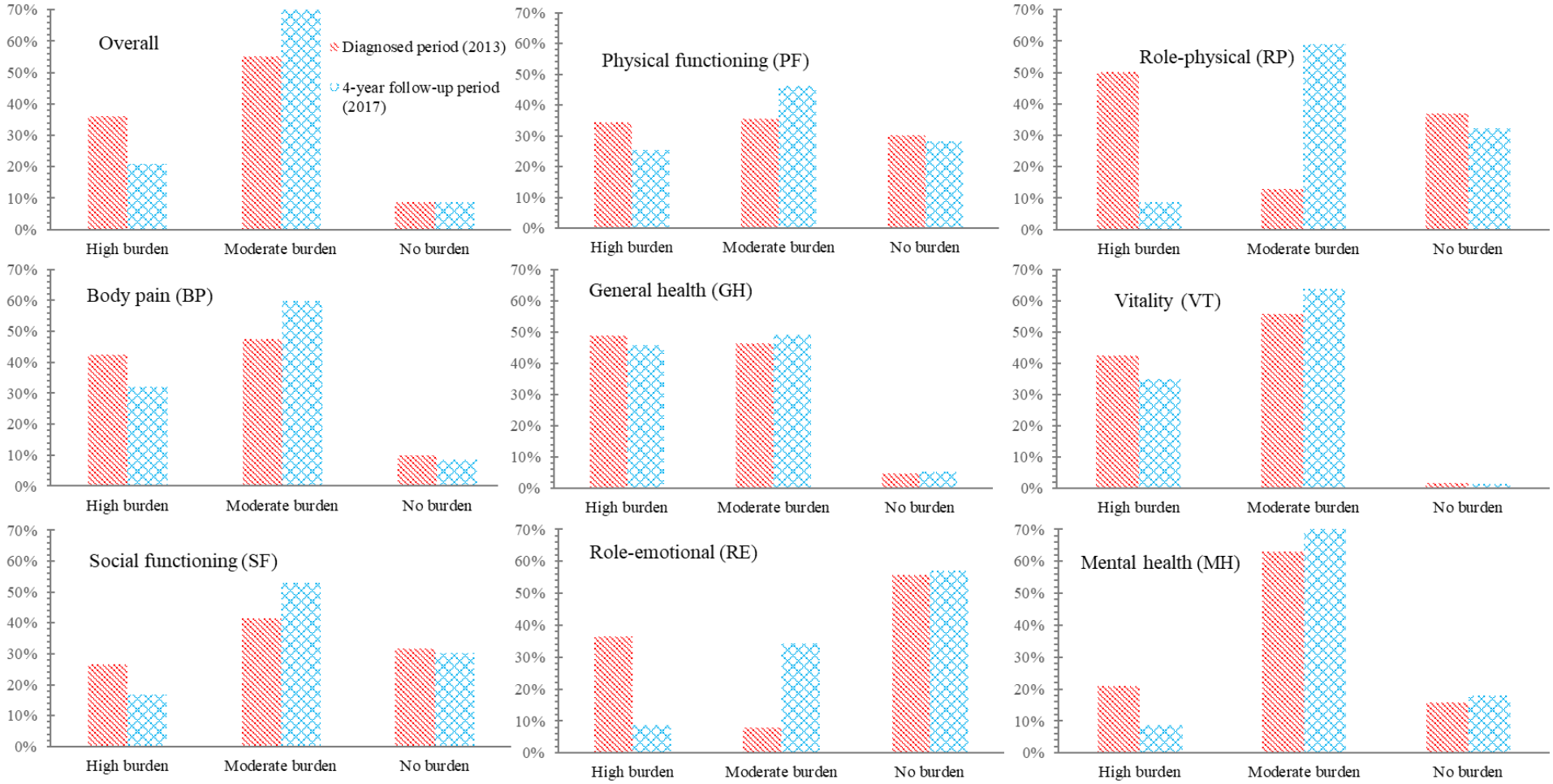

Table 3. Factors influencing in health status outcomes of cancer patients

Characteristics	Model 1	Model 2	Model 3	Model 4
	β (SE)	β (SE)	β (SE)	β (SE)
Female	1.82 (1.47)	1.29 (1.4)	2.11 (1.32)	2.09* (1.31)
Age	-0.03 (0.06)	-0.11* (0.06)	-0.08* (0.06)	-0.1 (0.06)
Educational attainment				
Year 11 or below (ref)	-	-	-	-
Year 12	**6.91 (2.99)	6.21** (2.78)	5.47 (2.54)	5.30** (2.45)
Trade/certificate/diploma	***6.92 (1.72)	6.39*** (1.66)	6.29*** (1.54)	6.11*** (1.52)
Tertiary	***10.29 (2.12)	8.20*** (2)	6.81*** (1.98)	5.96*** (1.99)
Unemployed (ref = employed)	-6.28*** (1.73)	-3.90** (1.88)	-1.81* (1.75)	-1.53 (1.74)
Marital status				
Single (ref)	-	-	-	-
Married	4.66* (2.33)	1.13 (2.32)	1.25 (2.30)	1.70 (2.33)
Others (separated/divorced/widowed)	1.08 (2.51)	-0.13 (2.42)	1.05 (2.35)	1.20 (2.37)
Ethnic status (ref = Indigenous)	-14.81*** (4.14)	-11.09** (4.38)	-8.19* (4.63)	-7.54* (4.78)
Hours of sleep per week				
<6 hours (ref)	-	-	-	-
≥6 hours	5.41*** (1.55)	3.59** (1.48)	1.54** (1.40)	1.83** (1.41)
Physical activity status				
Low (ref)	-	-	-	-
Moderate	9.33*** (1.53)	8.03*** (1.49)	7.10*** (1.40)	7.30*** (1.40)
High	15.65*** (1.68)	13.36*** (1.67)	11.32*** (1.60)	11.63*** (1.59)
Life conditions, mean scores (SD)				
Satisfaction with household members		0.46 (0.41)	0.37 (0.41)	0.43 (0.41)
Satisfaction overall employment		0.35* (0.21)	0.10 (0.19)	0.09 (0.19)
Satisfaction financial situation		1.98*** (0.32)	1.27*** (0.31)	1.29*** (0.31)
Satisfaction with social supports		1.10*** (0.38)	0.92** (0.36)	1.04*** (0.36)
Uninsured (ref = insured)			-2.87* (1.39)	2.39** (1.39)
Prescription medication (ref = no)			-6.30*** (1.68)	-6.00*** (1.68)
Diagnosed with comorbidities (ref = no)				
Arthritis or osteoporosis (= yes)			-3.84*** (1.30)	-3.62*** (1.31)
Asthma (= yes)			-1.50 (1.71)	-0.58 (1.70)
Chronic bronchitis or emphysema (= yes)			-9.94*** (2.47)	-9.88*** (2.49)
Diabetes (= yes)			-4.61*** (1.80)	-4.83*** (1.79)
Heart /Coronary disease (= yes)			-4.26** (1.70)	-4.18** (1.70)
Depression or anxiety (=yes)			-8.21*** (1.63)	-8.30*** (1.64)
Other mental illness(= yes)			-16.15*** (2.62)	-15.40*** (2.56)
High blood pressure/hypertension (= yes)			-1.10 (1.42)	0.87 (1.42)
Obesity (= yes)			-1.91* (1.31)	1.63 (1.31)
Any other circulatory condition (= yes)			-0.69 (1.91)	0.19 (1.97)
Location				
Major cities (ref)				-
Inner regional				-2.57* (1.48)
Outer regional				-7.17*** (2.32)
Remote or very remote				1.79 (3.53)
Socioeconomic status				
Q_1 (lowest 20%) (ref)				-
Q_2				-0.97** (2.04)
Q_3				-1.36 (2.03)
Q_4				1.26** (2.07)
Q_5 (highest 20%)				1.49** (1.89)

***, ** and * denotes significant at 0.1%, 1% and 5% risk level respectively and Qi = ith wealth quintile (i =1, 2. . . 5; higher i represents a quintile with higher wealth), β = regression coefficient, SE = standard error, SD = standard deviation, ref= reference group

Table 4. Standardised betas of longitudinal generalized linear mixed models evaluating the association of predictors with HRQoL of cancer patients

Characteristics	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6	Model 7	Model 8
	Physical functioning (PF)	***Role-physical (RP)***	***Body pain (BP)***	***General health (GH)***	***Vitality (VT)***	***Social functioning (SF)***	***Role-emotional (RE)***	***Mental health (MH)***
	β (SE)	**β (SE)**	**β (SE)**	**β (SE)**	**β (SE)**	**β (SE)**	**β (SE)**	**β (SE)**
Female	0.15 (1.56)	1.22 (2.20)	1.05 (1.55)	2.91* (1.56)	1.41 (1.60)	3.58** (2.06)	7.29*** (2.54)	3.99** (1.72)
Age	-0.22* (0.07)	-0.28*** (0.09)	-0.02 (0.07)	0 (0.07)	-0.05 (0.08)	-0.12 (0.10)	-0.22* (0.12)	0.03 (0.09)
Educational attainment								
Year 11 or below (ref)	-	-	-	-	-	-	-	-
Year 12	8.59*** (2.92)	6.85* (4.11)	3.47 (3.09)	2.92 (3.05)	2.65 (3.12)	4.99 (3.91)	13.22*** (4.77)	4.47 (3.49)
Trade/certificate/diploma	7.50*** (1.84)	6.37*** (2.51)	4.75*** (1.76)	3.49** (1.77)	6.33*** (1.87)	8.61*** (2.42)	15.13*** (3.07)	6.92*** (2.10)
Tertiary	9.05*** (2.47)	6.10* (3.45)	3.23 (2.34)	2.65* (2.39)	8.72*** (2.33)	8.53** (3.10)	15.04*** (3.94)	8.35*** (2.49)
Unemployed (ref = employed)	-5.70** (2.04)	-0.75 (2.94)	-1.94 (1.97)	-1.03 (2.12)	1.65 (2.14)	0.04 (2.69)	-3.81 (3.26)	-1.13 (2.30)
Marital status								
Single (ref)	-	-	-	-	-	-	-	-
Married	1.95 (2.63)	1.46 (3.69)	-2.39 (2.69)	-1.9 (2.72)	2.98 (2.76)	3.11 (3.65)	6.77 (4.37)	3.47 (3.11)
Others (separated/divorced/widowed)	-0.14 (2.71)	2.69 (3.72)	-1.13 (2.76)	-0.22 (2.77)	1.97 (2.82)	1.65 (3.70)	4.19 (4.44)	0.93 (3.21)
Household sizes								
<3 members (ref)	-	-	-	-	-	-	-	-
3 to 4 members	0.38 (2.17)	-0.31 (3.14)	-0.51 (2.20)	-2.74 (2.16)	-2.23 (2.28)	-3.59 (2.91)	-7.23* (3.59)	-2.23 (2.49)
≥ 5 members	4.35 (3.63)	9.19* (4.51)	3.40 (3.37)	4.24 (3.37)	0.83 (3.32)	1.36 (4.43)	5.14 (5.07)	0.55 (3.69)
Ethnic status (= Indigenous)	-3.52 (5.11)	-6.87 (8.52)	-12.02** (5.44)	-6.04 (5.58)	-13.03** (5.08)	-16.51** (6.45)	-16.11* (9.66)	-15.09** (6.95)
Hours of sleep per week								
<6 hours (ref)	-	-	-	-	-	-	-	-
≥6 hours	1.48* (1.72)	2.84* (2.45)	2.03* (1.66)	2.88** (1.61)	3.38** (1.74)	2.57* (2.26)	1.17* (2.92)	1.55* (1.92)
Physical activity status								
Low (ref)	-	-	-	-	-	-	-	-
Moderate	11.84*** (1.63)	10.61*** (2.47)	6.85*** (1.68)	4.42*** (1.59)	5.59*** (1.73)	10.85*** (2.28)	10.16*** (2.92)	3.10* (1.92)
High	15.28*** (1.89)	17.02*** (2.75)	10.31*** (1.84)	11.01*** (1.76)	10.52*** (1.95)	16.54*** (2.51)	14.30*** (3.19)	4.99*** (2.07)
Life conditions, mean scores (SD)								
Satisfaction with household members	0.33 (0.55)	1.12 (0.70)	-0.46 (0.49)	0.83 (0.52)	0.90** (0.50)	1.08 (0.66)	0.49 (0.81)	0.92 (0.58)
Satisfaction overall employment	0.39* (0.22)	0.15 (0.34)	0.05 (0.21)	-0.09 (0.23)	0.05 (0.24)	0.23 (0.31)	0.03 (0.38)	-0.43 (0.27)
Satisfaction financial situation	0.74* (0.38)	1.26** (0.51)	1.71*** (0.36)	0.96*** (0.37)	0.95*** (0.40)	1.46*** (0.51)	2.21*** (0.63)	1.72*** (0.44)
Satisfaction with social supports	0.76* (0.45)	0.47 (0.63)	1.48*** (0.46)	0.86** (0.44)	0.89** (0.46)	1.21*** (0.59)	1.37** (0.79)	1.03* (0.54)
Uninsured (ref = insured)	-1.65 (1.70)	-3.72* (2.35)	-3.36* (1.65)	-2.84* (1.68)	-1.83 (1.72)	-1.74 (2.20)	-4.00 (2.80)	-2.21* (1.92)
Prescription medication (ref = no)	-5.7*** (1.92)	-10.10*** (2.94)	-5.81*** (1.88)	-8.83*** (1.96)	-6.39*** (2.04)	-6.92*** (2.52)	-5.33* (3.12)	-3.96* (2.06)
Diagnosed with comorbidities (ref = no)								
Arthritis or osteoporosis (= yes)	-6.33*** (1.57)	-9.79*** (2.34)	-8.44*** (1.61)	-1.69 (1.55)	-0.09* (1.59)	0.35 (2.07)	0.45 (2.74)	1.10 (1.77)
Asthma (= yes)	-2.99 (2.18)	1.20 (2.93)	-1.23 (1.96)	-1.67 (1.87)	-0.77 (2.07)	0.89 (2.78)	0.65 (3.51)	0.06 (2.45)
Chronic bronchitis or emphysema (= yes)	-10.82*** (2.85)	-12.29*** (3.59)	-5.89* (2.92)	-11.68*** (2.89)	-8.72*** (3.24)	-11.18*** (4.32)	-15.79*** (5.14)	-8.05* (4.00)
Diabetes (= yes)	-4.20*** (2.30)	-3.74 (2.91)	-2.38 (2.12)	-5.51** (2.07)	-4.58*** (2.33)	-5.13* (2.99)	-8.84*** (3.93)	-5.50** (2.57)
Heart /Coronary disease (= yes)	-5.62*** (2.03)	-4.6 (2.88)	-2.17 (2.15)	-5.83*** (2.00)	-6.06*** (2.26)	-8.72*** (2.95)	-2.97 (3.71)	-5.15** (2.54)
Depression or anxiety (=yes)	-2.77 (1.97)	-6.77*** (2.72)	-3.40* (1.93)	-6.34*** (1.99)	-6.96*** (1.94)	-8.83*** (2.62)	-19.13*** (3.53)	-11.98*** (2.23)
Other mental illness(= yes)	-15.69*** (4.21)	-19.01*** (4.51)	-15.52*** (3.17)	-9.97*** (4.39)	-17.39*** (4.24)	-24.92*** (5.27)	-28.72*** (6.06)	-16.78*** (5.43)
High blood pressure/hypertension (= yes)	-0.38 (1.74)	-4.12* (2.42)	-2.5 (1.71)	-1.13 (1.72)	-1.50 (1.80)	2.90 (2.30)	-5.22** (2.87)	-0.62 (1.99)
Obesity (= yes)	-0.29 (1.67)	2.39 (2.49)	-0.96 (1.69)	1.21 (1.57)	-5.47*** (1.50)	-7.49** (2.03)	-5.78*** (2.69)	-10.20*** (1.60)
Any other circulatory condition (= yes)	-2.47 (2.76)	3.42 (3.32)	3.04 (2.62)	-2.39 (2.40)	1.68 (2.29)	1.37 (3.20)	-2.87 (4.79)	2.72 (2.87)

(Continued)

Table 4. (Continued)

Characteristics	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6	Model 7	Model 8
	Physical functioning (PF)	***Role-physical (RP)***	***Body pain (BP)***	***General health (GH)***	***Vitality (VT)***	***Social functioning (SF)***	***Role-emotional (RE)***	***Mental health (MH)***
	β (SE)	**β (SE)**	**β (SE)**	**β (SE)**	**β (SE)**	**β (SE)**	**β (SE)**	**β (SE)**
Location								
Major cities (ref)	-	-	-	-	-	-	-	-
Inner regional	-0.48 (1.80)	-8.89*** (2.48)	-1.12 (1.79)	-0.76 (1.82)	-1.10 (1.80)	-3.62 (2.32)	-5.81** (2.96)	-0.57 (1.98)
Outer regional	-5.48* (2.79)	-10.09*** (3.57)	-7.70*** (2.44)	-4.57* (2.62)	-4.42** (2.89)	-7.60*** (3.79)	-16.09*** (4.85)	-4.00 (3.35)
Remote or very remote	-2.87 (4.64)	2.60 (6.29)	6.83* (3.37)	0.77 (4.69)	-1.97 (4.41)	0.31 (6.02)	-6.01 (9.25)	-3.26 (5.18)
Socioeconomic status								
Q_1 (lowest 20%) (ref)	-	-	-	-	-	-	-	-
Q_2	0.06** (2.36)	1.52 (3.05)	-0.76 (2.18)	1.43 (2.32)	2.28 (2.30)	1.48 (3.03)	1.23 (3.96)	0.27 (2.65)
Q_3	0.39 (2.52)	-4.39 (3.43)	-1.83 (2.45)	2.28 (2.50)	1.28 (2.54)	1.93 (3.29)	3.92 (4.31)	0.35 (2.82)
Q_4	-2.46 (2.38)	-2.86 (3.34)	-1.85 (2.46)	-0.66 (2.54)	-0.38 (2.49)	0.85 (3.24)	-2.14 (4.28)	-0.50 (2.86)
Q_5 (highest 20%)	2.25* (2.54)	-0.6 (3.44)	-0.27 (2.57)	2.56 (2.56)	0.14 (2.50)	4.41 (3.36)	0.50 (4.17)	-1.01 (2.76)

Note: ***, ** and * denotes significant at 0.1%, 1% and 5% risk level respectively and Qi = ith wealth quintile (i =1, 2. . . 5; higher i represents a quintile with higher wealth), β = regression coefficient, SE = standard error, SD = standard deviation, ref= reference group.

In addition, this study also investigated health scores across the *SF-36* subscales including physical functioning, role-physical, body pain, general health, vitality, social functioning, role-emotional, and mental health. The model was also used to find the important parameters for predicting the quality of life of cancer survivors in a separate model for subscales (Table 4). These results closely followed the overall health status scores and showed the statistical significance of almost all the determined parameters outlined above.

Discussion

This study used cancer survivors' self-reported health status scores to examine the longitudinal course of patients in Australia and determine influencing factors that predicted their health status. Overall, the cancer survivors experienced improved health status outcomes over the four years following their diagnosis. Significantly this applied in particular to health states such as body pain, social functioning and mental health. While most cancer survivors recovered well over time, a considerable subgroup endured a long-term health burden. It is therefore argued that early interventions, including palliative care, which can improve the overall quality of life of people with cancer are of utmost significance. In this context, social cognitive theory-based interventions may be most salient [31], and a pivotal role should thus be afforded to cognitive, vicarious, self-reflective and self-regulatory factors and their impact on human adaptation and change. Advanced treatment targets comprising outcome expectations, self-efficacy, and self-regulation were significantly associated with better health status [14,32].

Approximately three-quarters of cancer survivors experienced at least one comorbidity condition with about 45% of cancer survivors having two or three comorbidities and this latter group had the largest negative association with health status. Other studies have confirmed that a significant number of cancer survivors are exposed more than one comorbidity condition and that this significantly and negatively influences their quality of life score [19,20]. However, cancer survivors' unhealthy lifestyles including tobacco use, poor diet and lack of access to preventative care significantly contributes to a higher risk of chronic illness including respiratory diseases, heart disease, stroke, diabetes, and obesity. The number of comorbid conditions, along with their severity, also impedes early cancer detection, course of treatment, prognosis, and survival outcomes [33]. The measured burden of

comorbid conditions of people with cancer significantly and negatively impacts on quality of life outcomes in different settings, including Australia [12,19,20]. Regional cancer survivors reported worse health status outcomes compared with patients who lived in major cities. Considerable evidence showed that geographically disadvantaged cancer survivors experienced significantly worse health status compared with other Australians [34–36].

These findings were in contrast to other studies [9,11], in which it was found that cancer survivors who survived with cancer in regional areas appeared to have an overall better quality of life. This situation may depend on access to healthcare facilities and the structure of healthcare service delivery. In Australia, cancer care services across the states are centralised in nature which disadvantages non-urban patients (e.g., regional or remote) who need to travel frequently for oncology follow-up treatments (e.g., chemotherapy and radiotherapy) at secondary or tertiary level health facilities. In this context, regional cancer patients face an additional challenge to receive cancer care due to their locations and the associated costs of transport as well as being reliant on caregiver support to access care [34,37]. Difficulty in accessibility and availability of appropriate healthcare services are challenges for all residents in regional and remote Australia with approximately 30% of the population living outside the major cities in Australia [38]. The national government is devoted to improving the cancer infrastructure by developing a structured network of new and improved cancer centres in regional Australia [39]. There is also a growing interest in the advanced technology-based model of service delivery in oncology. Technology-based models (e.g., tele-oncology) have been conducted in Western Australia and North Queensland, helping regional cancer patients to access healthcare services (e.g., specialist consultation, and therapeutic treatments) [40, 41]. Thus, the benefits of specialist support for an ongoing course of cancer treatment with high-level satisfaction and acceptance of services can lead to improved health status for cancer survivors living in regional areas [40, 41].

This study also found that engagement in moderate or adequate physical activities was related to a better quality of life which is consistent with previous study findings in that cancer survivors who had higher levels of physical activity had better health status [42]. Some studies have proven that physical exercise-related therapy can reduce fatigue and ensure better quality of life outcomes for cancer survivors [15,42].

Cancer patients or cancer survivors might improve their physical strength through proper exercise, which in turn increases acceptance of physical fatigue and metabolic efficiency which can change the characteristics of skeletal muscle, increase the number of oxidative fibers, or cause a decline in the number of glycolytic fibers [43]. Oxidative fibers can eradicate lactate from blood which reduces fatigue levels. Thus, increased muscle efficiency explains how patients with increased levels of physical activity can carry out normal daily activities with less fatigue [15].

Finally, the patterns of cancer survivors' life satisfaction-related factors decisively predicted higher health status scores over the period. Life satisfaction was conceptualised as the outcome of an individual's judgment about the extent of their current quality of life according to their self-imposed life behaviours. Previous studies have consistently concluded that life satisfaction factors predominantly contribute to quality of life outcomes [10,21]. The quality of life outcomes of patients in terms of life satisfaction trajectories may vary, i.e. both decline and increase over time, but they seem to return mostly to their full health state [10]. In this context, financial satisfaction is crucial to the outcome of cancer treatments which is usually very expensive, and often involves large out of pocket payments and reduce cancer patients' socioeconomic position. Life satisfaction may respond to changes (e.g., cancer diagnosis), but it is usually a temporary phenomenon [44]. This expression of an individuals' resilience following a cancer diagnosis helps explain the return to a more normal sense of life satisfaction after their cancer experience.

The present study did have some limitations. Study participants were derived from the *HILDA* survey covering the health, economic, employment, income and health characteristics of household members aged 15 years and older. Children who suffered from cancer were not included in this study. This study considered the overall health status of cancer survivors, which might vary in terms of cancer stages and types of cancer. The authors were not able to measure the cancer-specific health status of cancer patients due to the paucity of available information. The study findings were based on self-reported information that might have been impacted by respondents' prejudice (e.g., silence and over-response), or due to problems in understanding and interpretation. However, the key strengths of this study include the prospective design of long term follow up, and the application of well-validated

and reliable longitudinal wave measures of the impacts of cancer diagnosis on the quality of life.

Conclusions

Overall, the self-reported health status of cancer survivors improved over the period. The findings of this study could help policymakers to design new health interventions to address some of the contributing factors to the poor health status for cancer patients in Australia. This might include promoting adequate access to quality cancer care and exercise during treatment. These initiatives might directly or indirectly influence better health status of cancer survivors. The present results add to the ongoing body of evidence about the heterogeneous nature of individual adjustments after cancer diagnosis and further highlight the importance of considering inter-individual differences in research with this population group, as well as in planning service delivery. Life satisfaction appears in this population group to be temporally stable, and this may reflect individuals' psychological resilience during their cancer experience. There is a growing recognition of the importance of patient-focused outcomes in cancer care [44], whereby the quality of a person's life and the personal preferences and values of that person guide their health care. The inclusion of quality of life in future research, as a distinct adjustment outcome based on the individual's point of reference, is therefore warranted.

Abbreviations

IRSD: The index of relative socio-economic disadvantage

SES: Socioeconomic status,

MET: Metabolic Equivalent of Task

SF-36: Short form

HILDA: Household, Income and Labour Dynamics in Australia

HRQoL: Health-Related Quality of Life

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Conflicts of interest

The authors declare that they have no conflict of interest.

Author Contribution(S)

Conceptualized the study: RAM; Contributed data extraction and analyses: RAM. Result interpretation: RAM. Prepared the first draft: RAM. Contributed during the conceptualization and interpretation of results and substantial revision: RAM, KA, JD and JG. Revised and finalized the final draft manuscript: RAM, KA, JD and JG. All authors read and approved the final version of the manuscript.

Ethical Approval

The Household, Income and Labour Dynamics in Australia (HILDA) data are used under strict licensing. Data can be potentially obtained and shared subject to a peer reviewed application. Ethical approval for the HILDA study was obtained from the Faculty of Business and Economics Human Ethics Advisory Committee at the University of Melbourne (#1647030). Approval for the use of HILDA data was provided by the Department of Social Services. Ethical approval was not required from an institutional review board because the patient information was de-identified. Appropriate approval was obtained for this study from the Department of Social Services to access the de-identified longitudinal dataset.

Data sharing statement:

This paper uses unit record data from the Household, Income and Labor Dynamics in Australia (HILDA) Survey. The data are available from the Australian Government Department of Social Services and the Melbourne Institute of Applied Economic and Social Research at https://melbourneinstitute.unimelb.edu.au/hilda.

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2.3 Study 3

Cancer burden: Long-term chronic comorbid conditions and consequences

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The *second study* of this thesis examined longitudinal measures in health status burden among cancer patients and its associated predictors. Study 3 investigated the long-term chronic comorbid conditions in terms of disease pattern along with potential predictors among cancer patients and consequences over an extended period.

Article III: The burden of chronic diseases among Australian cancer patients: Evidence from a longitudinal exploration, 2007-2017

The objective of *Study 3* was to investigate the distribution of burden of chronic comorbid conditions and associated predictors among cancer patients in Australia over the period of 2007-2017. This study found that sixty-one percent of cancer patients experienced at least one chronic disease over the period, and 21% of patients experienced three or more chronic diseases. This study determined that advancing age, inadequate levels of physical activity, patients who suffered from extreme health burden or moderate health burden, and patients living in the poorest households were significant predictors associated with a higher risk of chronic comorbid conditions. This study concludes that a large number of cancer patients experience an extreme burden of chronic comorbid conditions and the different dimensions of these in cancer survivors have the potential to affect the trajectory of their cancer burden. It is also significant for health care providers, including physical therapists and oncologists, who must manage the unique problems that challenge this population and who should advocate for prevention and evidence-based interventions.

PLOS ONE

RESEARCH ARTICLE

The burden of chronic diseases among Australian cancer patients: Evidence from a longitudinal exploration, 2007-2017

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Abstract

Introduction

Cancer is a major public health concern in terms of morbidity and mortality worldwide. Several types of cancer patients suffer from chronic comorbid conditions that are a major clinical challenge for treatment and cancer management. The main objective of this study was to investigate the distribution of the burden of chronic comorbid conditions and associated predictors among cancer patients in Australia over the period of 2007–2017.

Methods

The study employed a prospective longitudinal design using data from the Household, Income and Labour Dynamics in Australia survey. The number of chronic comorbid conditions was measured for each respondent. The longitudinal effect was captured using a fixed-effect negative binomial regression model, which predicted the potential factors that played a significant role in the occurrence of chronic comorbid conditions.

Results

Sixty-one percent of cancer patients experienced at least one chronic disease over the period, and 21% of patients experienced three or more chronic diseases. Age (>65 years old) (incidence rate ratio, *IRR* = 1.15; 95% confidence interval, *CI*: 1.05, 1.40), inadequate levels of physical activity (*IRR* = 1.25; 95% CI: 1.09, 1.59), patients who suffered from extreme health burden (*IRR* = 2.30; 95% CI: 1.73, 3.05) or moderate health burden (*IRR* = 1.90; 95% CI: 1.45, 2.48), and patients living in the poorest households (*IRR* = 1.21; 95% CI: 1.11, 1.29) were significant predictors associated with a higher risk of chronic comorbid conditions.

strict licensing. Although data are not available to the public, they can be potentially obtained and shared subject to a peer-reviewed application. The data are available from the Australian Government Department of Social Services and the Melbourne Institute of Applied Economic and Social Research at https://melbourneinstitute.unimelb.edu.au/hilda.

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Conclusions

A large number of cancer patients experience an extreme burden of chronic comorbid conditions and the different dimensions of these in cancer survivors have the potential to affect the trajectory of their cancer burden. It is also significant for health care providers, including physical therapists and oncologists, who must manage the unique problems that challenge this population and who should advocate for prevention and evidence-based interventions.

Introduction

Cancer is one of the most pressing public health problems worldwide [1]; an estimated 9.6 million patients die from cancer each year. In Australia, it is also an alarming issue with the health system dealing with 483 new cases per 100,000 people in 2019, while on average 136 people die from cancer each day [2]. Cancer contributes 18% of the total burden of disease in terms of disability-adjusted life years, followed by 14% from cardiovascular diseases, 13% from musculoskeletal conditions, and 12% from mental and substance use disorders in Australia [3]. Further, there are approximately one million survivors in Australia who have been diagnosed with cancer in the past [4]. The five-year survival from all cancers combined improved from 48% to 69% between 1990 and 2011–2015 [2].

However, the majority of cancer patients suffer from chronic diseases or conditions, commonly referred to as comorbidity. The risk of having comorbidity increases during treatment as well as oncology follow-up periods [3,5,6], which adversely influences treatment choices and outcomes. Chronic comorbid conditions of cancer patients contribute to a major clinical challenge in terms of cancer diagnosis, ill health, the course of treatment, long-term disability and disease management [7]. In 2014–15, more than 11 million Australians (50%) reported having at least one chronic disease, wherein approximately 1 in 4 (23%) Australians had two or more chronic conditions [8]. This rate was more pronounced for people aged 65 and over (87%) compared with people aged 0–44 (35%), females (52%) compared with males (48%), people in disadvantaged socioeconomic areas (55%) compared with those in the most advantaged socioeconomic areas (47%), and people living in regional and remote areas (54%) compared with those in the major cities (48%) [8]. Ultimately, the severity of comorbidity leads to an increased risk of hospitalisation, reduced health status, increased mortality, and increased financial burden on the healthcare system [9–11]. It may also adversely impact an individual's access to advanced cancer treatments (e.g., chemotherapy and radiotherapy) and the effectiveness of that treatment [12]. This is a substantial prognostic factor for the long-term survival of cancer patients. There is a growing body of research on the significant impact of chronic comorbid conditions among patients with cancer. However, there are limited empirical studies on comorbidities available in the Australian setting [7,13–15].

Comorbidity has a well documented detrimental effect on cancer survival [9] and it describes the existence of a long-term health condition or disorder in the presence of primary disease or illness [16]. In the case of cancer, chronic comorbidity refers to the existence of one or more comorbid conditions in a person simultaneously. While the existence of these comorbid health conditions may be extraneous, particularly chronic diseases, there is an association between them. Further, many chronic diseases share common risk factors. Cancer patients with comorbid conditions also experience a higher physiological burden of disease [7]. The presence of specific severe comorbidities or psychiatric disorders is associated with delayed

cancer diagnosis [11]. Further, patients with chronic diseases with regular medical consultations and follow-up had their cancer detected at an earlier stage [12].

The chance of improving health status and completing a course of cancer treatment in the presence of comorbidities is significantly lower among cancer patients [4,13,15,17,18] and is associated with a higher rate of mortality depending on the severity of disease and associated comorbidity [11]. For instance, the mortality rate is substantially higher among cancer patients with comorbidities (47%) compared with cancer patients without comorbidities (34%) [19]. Given the clinical significance of comorbidity and its high prevalence in cancer survivors, it is essential to have a measure for quantifying likely effects on cancer outcomes [20]. Understanding more about comorbidities among cancer patients can generate possible evidence as well as provide direction for prevention, management, and treatment of chronic diseases.

A number of studies confirm that comorbid chronic conditions were more pronounced among cancer patients [4,11,13–15,21,22]. The most prevalent risk factors were age (over 65 years) [23,24], unhealthy behaviors (e.g., alcohol consumption and smoking tobacco) [25,26], obesity, limited engagement with physical activity [27] and inadequate diet [25] and they are significantly related to a higher risk of developing cancer along with multiple chronic diseases [5,7,25]. Further, comorbid conditions of cancer patients are significantly associated with worse health status during treatment and oncology follow-up periods [28,29] as well as low or intermediate socioeconomic status [30], and poor nutritional status [31]. The ongoing evidence shows that modifying or avoiding risk factors can significantly reduce the burden of chronic comorbid conditions among cancer patients [1]. For example, cancer survivors who engage in less sedentary behavior enjoy a better quality of life [32], and this can also significantly contribute to reducing the risk of experiencing chronic comorbid conditions [33].

The primary intention of these studies was to examine the distribution, trend, pattern, and disparity in comorbidity status among cancer patients when considering a limited range of variables. The majority of these studies pay little attention to examining the long-term impact of chronic comorbid conditions for cancer survivors' over times. Therefore, routine oncology follow-ups must explore how cancer survivors' characteristics impact on the number of chronic comorbid conditions they experience.

This study will examine the longitudinal nature of chronic comorbid conditions of cancer patients. More specifically, the study proposes to develop a better understanding of the longitudinal distribution of chronic comorbidity status among cancer patients as well as its impact over time. This study complements and contributes to this strand of ongoing cancer research to increase awareness and improve public health practice among sufferers and survivors, and to measure impact. The findings could contribute to designing appropriate interventions and/or the provision of quality healthcare services and resources for ongoing surveillance of people living with, through and beyond cancer, and help determine what kinds of support survivors need. This study, therefore, aims to investigate the distribution, potential predictors and associated burden of chronic comorbid conditions among cancer patients by using a longitudinal data set from the Household, Income and Labour Dynamics in Australia (*HILDA*) survey.

Materials and methods

Study design

The study design is a longitudinal exploration using a household-based panel over an extended period of 2007 to 2017. Individuals who face the burden of life-threatening cancer were interviewed with a focus on the magnitude of the cancer burden associated with their chronic comorbid conditions. The magnitude of the cancer burden includes their course of treatment

over an extended oncology follow-up period which can affect their health status burden and includes chronic comorbid conditions, disability, and adverse events.

Conceptual framework

The distribution of comorbidity varies by patient-level factors (Fig 1). Like cancer itself, it increases with age. Functional status, a measure of patients' ability to perform everyday activities, is related to both the presence and the consequences of chronic comorbid conditions. Health status burden is associated with increased vulnerability to stressors that result from decreased health scores as well as physiological strength [34]. Further, health status burden is strongly associated with increased age and the severity of the disease. In the context of comorbidity experiences, patients assess their health status depending on the severity of disease (as either better or worse) [35]. Despite strong associations between them, comorbidity, functional status, and health status burden are separate entities, and each has an independent effect on outcomes [34]. To investigate the longitudinal effects, it is assumed that several predictors (e.g., individual background characteristics, social factors, and disease-related symptomatic factors), measured at the symptom-level might predict outcome factors (e.g., appraisal of disease severity levels, utilisation of advanced treatment, life satisfaction, and uncertainty). Moreover, the combination of predictors was expected to predict patients' health outcomes (e.g., chronic comorbid conditions, long-term health problems or disability, and adverse events).

Data source

Data came from the Household, Income and Labour Dynamics in Australia (*HILDA*) survey [36]. The *HILDA* survey commenced in 2001 and is a nationally representative household-based panel study that produces data on the lives of Australian residents aged 15 or over. As per the *HILDA* protocol, written or verbal consent was collected from all potential participants before conducting the survey. Data were collected through face-to-face interviews using quantitative survey instruments, followed by re-interviews with the same people in subsequent years. The details of the methods of data collection, including the sampling technique, have been explained elsewhere [36]. The present study participants were diagnosed with cancer patients,

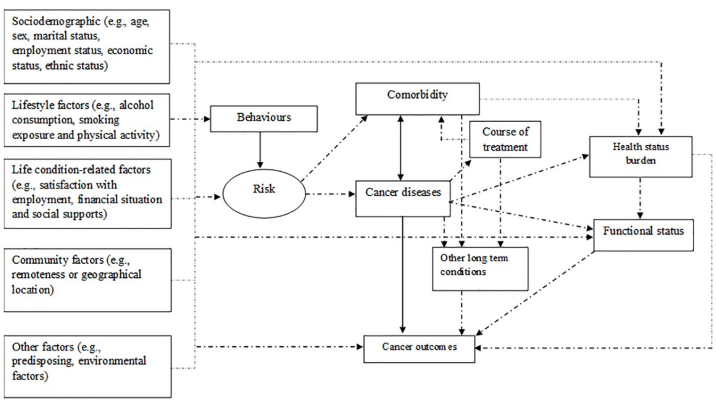

Fig 1. Conceptual framework of the study.

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and data were restricted to four waves (e.g., wave-7, wave-9, wave-13 and wave-17) based on the availability of data related to cancer. However, wave-3 was excluded from the analysis due to the limited data related to comorbidity status. Other survey waves were excluded from the analyses due to the paucity of cancer-related information. A total of 2,066 diagnosed cancer patients were potential study participants from the four waves: wave-7 in 2007 ($n_2 = 557$), wave-9 in 2009 ($n_3 = 416$), wave-13 in 2013 ($n_4 = 517$) and wave-17 in 2017 ($n_5 = 576$).

Study variables

Outcome variable. The chronic comorbid conditions were classified into disease groupings and cover the most common types of long-term health conditions experienced by cancer patients in the Australian community. A previous review study identified that at least 21 approaches have been executed to measure comorbidity status [37]. There is no gold-standard method for measuring comorbidity among cancer populations [37]. The selection of the method depends on the study research question, data availability, and population studied. A number of methods related to measuring comorbidity status have been used in the context of cancer-related studies including exploration of the impact of single conditions (such as diabetes or congestive heart failure) [38–40], single condition counts [41–43], weighted indices [43–47], and organ-based systems [48–50]. Although all these approaches aim to evaluate the same underlying construct, they vary in terms of the study purpose for which the measures were performed. These approaches vary in the context of study perspective and design. The simplest approach to measuring comorbidity status is to investigate the distribution of individual comorbid conditions and to treat them independently and/or to combine them by summing the total number of conditions [51]. In this study, a single condition count approach was performed to measure comorbidity status. Cancer patients reporting chronic condition(s) were considered an outcome variable in the analysis. Chronic comorbid conditions included being diagnosed with serious chronic illness, including arthritis or osteoporosis, heart disease, diabetes, hypertension, mental illness, or circulatory conditions. The count of chronic health conditions was measured for each respondent based on the number of disease exposures and who had been prescribed medication for their illness. If the respondents had multiple chronic conditions, it was counted as multiple responses.

Explanatory variables. This study considered several demographic, socio-economic and health and lifestyle-related variables based on the conceptual framework, as putative predictors of chronic comorbid conditions. Socio-demographic factors, such as sex, age, educational achievement, employment status, and marital status were considered as potential factors in the analysis. Lifestyle factors such as alcohol consumption, smoking exposure, and physical activity were also included. The level of physical activity was categorized into three groups as low, moderate, or high [27,52,53]. Further, life condition-related factors such as satisfaction with employment, financial situation, and social supports were also selected as potential predictors. Ethnic status was defined as Aboriginal or non-Aboriginal. The quality of life scores was measured using the medical outcomes study short-form (*SF-36*) [54]. The SF-36 is one of the most common generic measures of health-related quality of life, which is widely used to assess the burden of disease in the context of different country settings [55]. It uses psychometric properties to enable profiling of physical functional health and well-being and to quantify disease burden across eight domains, including physical functioning, role-physical, body pain, general health, vitality, social functioning, role-emotional, and mental health. Considering these dimensions, the total score on each *SF-36* subscale ranges between 0 and 100, labelling 'worst imaginable health' and 'best imaginable health state', respectively. It is signified that the higher scores represent better health status. A recent review study confirmed that several studies used a total score of *SF-36* items to derive quality of life scores across the eight domains of *SF-36*

[56]. The levels of health status burden were proposed based on the magnitude of quality of life scores as follows: (1) high burden if the short form-36 (*SF-36)* scores < 50.00, (2) moderate burden if $50.00 \leq$*SF-36* scores < 90.00, and (3) no burden if *SF-36* scores ≥ 90.00. The level of health status burden captured the severity of disease for cancer patients. Work disability was measured based on the severity of disability score ranged from 0 to 10, with 10 indicating 'able to do any work' and 0 indicating 'not at all'. The severity of disability level was defined as follows: (i) 'no disability' if disability score was equal to zero, (ii) 'moderate disability' for disability scores of 1 to 6, and (iii) 'severe disability' for disability scores of 7 to 10. Geographical locations were defined according to the accessibility to services and the Remoteness Index of Australia [57], and they were categorized into five groups: major cities, inner regional, outer regional and remote or very remote. The index of relative socioeconomic disadvantage (*IRSD*) was used to measure socioeconomic status (*SES*). The index was defined into five groups with these threshold values: Q_1 (*IRSD* ≤ 927.0), Q_2 ($927.0 >$ IRSD ≤ 965.8), Q_3 ($965.8 >$ *IRSD* ≤ 1001.8), Q_4 ($1001.8 >$ *IRSD* ≤ 1056.0), or Q_5 (*IRSD* > 1056.0) [58]. This is a geographical area-based estimate of socioeconomic status using income, education level and occupation where communities are categorised from economically disadvantaged to wealthy.

Statistical analysis

This study utilised descriptive analyses to compare patients with cancer and chronic medical conditions across the characteristics. The trend of chronic comorbid conditions among cancer patients was performed using the Cochran-Armitage trend test [59]. In the analytical exploration, the adjusted fixed-effect negative binomial regression model was used to identify the potential factors that had a significant role in the exposure to chronic comorbid conditions. In the regression model, the dependent variable (number of chronic comorbid conditions) was characterised as a count measure. An unadjusted analysis was performed using only separated explanatory variables for the following reasons: (1) primary screening of the selection of qualified predictors, which were added in the adjusted model, (2) although the chi-square tests (or one-way analysis where appropriate) are only used to find the association between outcome and explanatory variables. However, the majority of the predictor variables were categorical nature with two or more labels in this study. Therefore, an un-adjusted analysis was performed to find the association between outcome and the labels of explanatory variables. The predictor variables were included in the adjusted model only if any label of the predictor was significant at 5% or less risk level in the unadjusted model, which in turn was used to adjust for the effects of other potential confounders. However, insignificant predictors were not included in the adjusted model. The model was tested for sensitivity by the forward selection procedure (e.g., including and excluding specific variables) with robust standard errors. For the independent variables, the category found to be least at risk of having chronic comorbid conditions in the analysis was considered as the reference for constructing incidence risk ratios (*IRR*). Statistical significance was considered at the 5% risk level. All data analyses were undertaken using the statistical software Stata/SE 13 (StataCorp, College Station, TX, USA).

Ethical considerations

The Household, Income and Labour Dynamics in Australia (*HILDA*) data are used under strict licensing. Data can be potentially obtained and shared subject to a peer-reviewed application. Ethical approval for the *HILDA* study was obtained from the Faculty of Business and Economics Human Ethics Advisory Committee at the University of Melbourne (#1647030). Approval for the use of *HILDA* data was provided by the Department of Social Services. Ethical approval was not required from an institutional review board because the patient information

was de-identified. Appropriate approval was obtained for this study from the Department of Social Services to access the de-identified longitudinal dataset.

Results

Background characteristics of the study population

A total of 2,066 cancer patients were potential participants (Tables 1 and 2). Approximately 54% of patients were male, with 58% of patients being married. A higher proportion (46%) of the patients were senior or old senior-aged (more than 65 years), followed by middle-aged (37%). Approximately 47% had completed middle or high school level education, with 316 cancer patients (15%) having tertiary education. Sixty three percent of 63% of patients were unemployed, while 45% of patients had inadequate physical activity, with only 23% of patients having high-level physical activities per week. Two-third of 75% of patients consumed alcohol frequently. The majority of participants (89%) reported a moderate or extreme health burden, whereas 42% of patients experienced moderate or severe disability levels. In addition, 72% received prescribed medication, and 61% lived in major cities.

Distribution and changes of chronic comorbid conditions with cancer patients over time

The prevalence of comorbid conditions was reported by cancer patients as follows: arthritis or osteoporosis (45%), high blood pressure or hypertension (39%), obesity (23%), depression or anxiety (22%), heart disease (14%), and asthma (13%). These were significantly increased in the prevalence of depression or anxiety ($p<0.01$), mental illness ($p = 0.052$) and obesity ($p = 0.003$) over the period (Fig 2). However, a downward trend in the prevalence of comorbid conditions was observed for arthritis/osteoporosis ($p = 0.012$) over time.

Overall, approximately 42% of patients suffered from one to two chronic comorbid conditions, while 21% of patients experienced at least three or more comorbid conditions (Table 1). The prevalence of comorbid conditions was prominently distributed by age. The majority of comorbidities were highly pronounced in patients due to a lack of physical activity. For example, 56% of patients were more likely to report three or more comorbid conditions. This prevalence was disproportionately low (14%) in those who engaged in a high level of physical activity. Further, patients who suffered from at least one comorbid condition were significantly aligned with the magnitude of high or moderate health status burden (e.g., 62% for severe burden and 36% for moderate burden). Similarly, an upward trend of the upper extremity of disability levels was observed with an increased number of comorbid exposures among the poorest cancer survivors during the period (Fig 3). Regarding socioeconomic position, the magnitude of comorbid conditions was more pronounced in the most disadvantaged socio-economic group. For example, 28% of patients who lived in the poorest households were significantly exposed to three or more comorbid conditions compared with the richest households (13%). Also, the severity of disability score was also highest among patients in the poorest households along with an increasing number of comorbid conditions (Fig 3).

Factors influencing chronic comorbid exposure of cancer patients

Table 3 exhibits the results of the fixed effect negative binomial regression analyses. In the adjusted model, older patients, the magnitude of health status burden associated with cancer, utilisation of healthcare, and patients living in the poorest households were significant predictors associated with a higher risk of comorbid conditions. An aged patient (>65 years old) has 1.15 times higher risk of having comorbid conditions (incidence rate ratio, *IRR* = 1.15; 95%

Table 1. Summary statistics by the number of chronic condition among cancer patients for wave 7 and wave 9.

Variables	Number of observations, n (%)	Wave-7			Wave-9		
		Number of chronic comorbid conditions, n (%)			Number of chronic comorbid conditions, n (%)		
		0	1–2	3 or more	0	1–2	3 or more
Sex							
Male	1,123 (54.36)	234 (54.80)	77 (59.23)	na	45 (51.14)	110 (48.46)	55 (54.46)
Female	943 (45.64)	193 (45.20)	53 (40.77)	na	43 (48.86)	117 (51.54)	46 (45.54)
Age							
<25 years	53 (2.57)	10 (2.34)	3 (2.31)	na	1 (1.14)	4 (1.76)	1 (0.99)
25–45 years	283 (13.70)	77 (18.03)	17 (13.08)	na	23 (26.14)	32 (14.10)	8 (7.92)
46–65 years	771 (37.32)	146 (34.19)	69 (53.08)	na	39 (44.32)	86 (37.89)	30 (29.7)
>65 years	959 (46.42)	194 (45.43)	41 (31.54)	na	25 (28.41)	105 (46.26)	62 (61.39)
Educational attainment							
Year 11 or below	774 (37.46)	169 (39.58)	48 (36.92)	na	26 (29.55)	97 (42.73)	46 (45.54)
Year 12	168 (8.13)	37 (8.67)	14 (10.77)	na	10 (11.36)	15 (6.61)	9 (8.91)
Trade/certificate/diploma	808 (39.11)	149 (34.89)	54 (41.54)	na	35 (39.77)	81 (35.68)	40 (39.6)
Tertiary	316 (15.30)	72 (16.86)	14 (10.77)	na	17 (19.32)	34 (14.98)	6 (5.94)
Unemployed	1,306 (63.21)	250 (58.55)	66 (50.77)	na	40 (45.45)	150 (66.08)	86 (85.15)
Marital status							
Single	258 (12.49)	52 (12.18)	20 (15.38)	na	16 (18.18)	27 (11.89)	7 (6.93)
Married	1,196 (57.89)	256 (59.95)	80 (61.54)	na	46 (52.27)	130 (57.27)	52 (51.49)
Others	612 (29.62)	119 (27.87)	30 (23.08)	na	26 (29.55)	70 (30.84)	42 (41.58)
Alcohol consumption (= yes)	1,500 (72.60)	341 (79.86)	102 (78.46)	na	64 (72.73)	158 (69.60)	66 (65.35)
Smoking exposure (= yes)	276 (13.36)	64 (14.99)	22 (16.92)	na	11 (12.50)	32 (14.10)	13 (12.87)
Physical activity status							
Low	876 (42.40)	153 (55.11)	88 (55.11)		36 (55.11)	98 (55.11)	52 (55.11)
Moderate	701 (33.93)	134 (29.55)	30 (29.55)		28 (29.55)	74 (29.55)	33 (29.55)
High	489 (23.67)	140 (15.34)	12 (15.34)		24 (15.34)	55 (15.34)	16 (15.34)
Health status burden							
No burden	208 (10.07)	57 (13.35)	13 (10.00)	na	24 (27.27)	19 (8.37)	1 (0.99)
Moderate burden	1,205 (58.33)	268 (62.76)	82 (63.08)	na	48 (54.55)	135 (59.47)	41 (40.59)
Severe burden	653 (31.61)	102 (23.89)	35 (26.92)	na	16 (18.18)	73 (32.16)	59 (58.42)
Disability status							
No disability	1,172 (56.73)	258 (60.42)	76 (58.46)	na	76 (86.36)	124 (54.63)	32 (31.68)
Moderate disability	509 (24.64)	92 (21.55)	26 (20.00)	na	7 (7.95)	63 (27.75)	39 (38.61)
Severe disability	385 (18.64)	77 (18.03)	28 (21.54)	na	5 (5.68)	40 (17.62)	30 (29.70)
Healthcare utilisation (= yes)	1,093 (72.43)	219 (65.45)	63 (46.95)	na	22 (25.00)	181 (79.74)	98 (97.03)
Life satisfaction with-							
Employment, mean (sd)	3.39 (3.96)	3.51 (4.03)	3.86 (3.94)	na	5.3 (3.98)	3.55 (3.98)	2.36 (3.88)
Financial situation, mean (sd)	6.73 (2.37)	7.05 (2.27)	6.65 (2.43)	na	6.98 (2.14)	6.63 (2.45)	6.04 (2.59)
Social supports, mean (sd)	7.83 (1.82)	8.09 (1.54)	7.97 (1.54)	na	7.91 (1.73)	7.64 (2.03)	7.78 (1.98)
Remoteness							
Major Cities	1,264 (61.18)	270 (63.23)	75 (57.69)	na	48 (54.55)	128 (56.39)	63 (62.38)
Inner Regional	519 (25.12)	98 (22.95)	34 (26.15)	na	24 (27.27)	59 (25.99)	24 (23.76)
Outer Regional	247 (11.96)	50 (11.71)	21 (16.15)	na	13 (14.77)	38 (16.74)	12 (11.88)
Remote or very remote	36 (1.74)	9 (2.11)	na	na	3 (3.41)	2 (0.88)	2 (1.98)
Socioeconomic status							
Q_1 (lowest 20%) (ref)	407 (19.70)	81 (18.97)	23 (17.69)	na	11 (12.50)	46 (20.26)	27 (26.73)

(*Continued*)

Table 1. (Continued)

Variables	Number of observations, n (%)	Wave-7			Wave-9		
		Number of chronic comorbid conditions, n (%)			Number of chronic comorbid conditions, n (%)		
		0	1–2	3 or more	0	1–2	3 or more
Q_2	470 (22.75)	87 (20.37)	27 (20.77)	na	16 (18.18)	60 (26.43)	29 (28.71)
Q_3	369 (17.86)	79 (18.50)	33 (25.38)	na	25 (28.41)	39 (17.18)	14 (13.86)
Q_4	428 (20.72)	98 (22.95)	28 (21.54)	na	20 (22.73)	39 (17.18)	21 (20.79)
Q_5 *(highest 20%)*	392 (18.97)	82 (19.20)	19 (14.62)	na	16 (18.18)	43 (18.94)	10 (9.90)
Overall	2,066 (100)	427 (76.66)	130 (23.34)	na	88 (21.15)	227 (54.57)	101 (24.28)

Na = not available

https://doi.org/10.1371/journal.pone.0228744.t001

confidence interval, *CI*: 1.08, 1.45) compared with a young patient (<25 years). Patients who performed lower levels of physical activity were 1.25 times more likely to have a chronic comorbid condition (*IRR* = 1.25; 95% CI: 1.09, 1.59) compared with patients who engaged in high-level physical activity. Further, patients who faced an extreme health burden were 2.30 times significantly higher risk of having comorbid conditions than those with no health burden. The risks of having a comorbid condition were more pronounced among patients who suffered from extreme health burden (*IRR* = 2.30 times) or moderate burden level (*IRR* = 1.90 times) compared with patients who reported excellent health status. Similarly, a higher risk of having a comorbid exposure was significantly observed in cancer patients who lived in the poorest households (*IRR* = 1.21; 95% CI: 1.11, 1.29) compared with their richest counterparts.

Discussion

The study results show that approximately 63% of cancer patients suffered from at least one chronic disease. The most prevalent comorbid conditions were arthritis or osteoporosis, high blood pressure or hypertension, obesity, depression or anxiety, heart disease, and asthma. However, these were significantly increased in the presence of diabetes, depression or anxiety, mental illness, heart disease and obesity over time. In the adjusted model, older patients, inadequate level of physical activities, the magnitude of health burden associated with cancer, utilisation of healthcare, and patients living in the poorest households were significant predictors associated with a higher risk of comorbid conditions.

Further, patients who faced an extreme health burden had a three times higher risk of having comorbid conditions than who reported excellent health status. Some studies have confirmed that the poor health status of cancer patients resulted in a greater burden of functional disability (e.g., specific task difficulties) [60,61] along with a higher burden of chronic diseases [15,30,62]. However, the prevalence of long-term health problems, including chronic illness, short or long-term disability, was also more concentrated in combination with a cancer diagnosis [63–68]. Advanced cancer treatments can damage healthy cells or organs [69], for example, radiation and chemotherapy may impose short and long-term chronic health problems and impact on the spinal cord, nerves, and brain, which then may significantly contribute to long-term adverse health outcomes like death, physical and mental disabilities.

The results indicate that aged cancer patients (older than 65 years) were at a 1.15 times higher risk of having chronic comorbid conditions compared with younger patients. This finding is consistent with previous studies, which revealed that elderly cancer patients reported significantly more exposure to chronic comorbid conditions [23,70,71], required more assistance with daily living activities [72], and had deficits in performing work-related activities in terms

Table 2. Summary statistics by the number of chronic condition among cancer patients for wave 13 and wave 17.

Variables	Wave-13			Wave-17			Overall		
	Number of chronic comorbid conditions, n (%)			Number of chronic comorbid conditions, n (%)			Number of chronic comorbid conditions, n(%		
	0	1–2	3 or more	0	1–2	3 or more	0	1–2	3 or more
Sex									
Male	70 (58.82)	122 (50.41)	87 (55.77)	73 (57.94)	160 (58.39)	90 (51.14)	422 (55.53)	469 (53.72)	232 (53.58)
Female	49 (41.18)	120 (49.59)	69 (44.23)	53 (42.06)	114 (41.61)	86 (48.86)	338 (44.47)	404 (46.28)	201 (46.42)
Age									
<25 years	6 (5.04)	9 (3.72)	2 (1.28)	6 (4.76)	5 (1.82)	6 (3.41)	23 (3.03)	21 (2.41)	9 (2.08)
25–45 years	25 (21.01)	30 (12.4)	9 (5.77)	26 (20.63)	28 (10.22)	8 (4.55)	151 (19.87)	107 (12.26)	25 (5.77)
46–65 years	51 (42.86)	93 (38.43)	47 (30.13)	56 (44.44)	98 (35.77)	56 (31.82)	292 (38.42)	346 (39.63)	133 (30.72)
>65 years	37 (31.09)	110 (45.45)	98 (62.82)	38 (30.16)	143 (52.19)	106 (60.23)	294 (38.68)	399 (45.7)	266 (61.43)
Educational attainment									
Year 11 or below	31 (26.05)	88 (36.36)	70 (44.87)	30 (23.81)	91 (33.21)	78 (44.32)	256 (33.68)	324 (37.11)	194 (44.8)
Year 12	9 (7.56)	20 (8.26)	8 (5.13)	12 (9.52)	21 (7.66)	13 (7.39)	68 (8.95)	70 (8.02)	30 (6.93)
Trade/certificate/diploma	51 (42.86)	107 (44.21)	59 (37.82)	47 (37.3)	117 (42.7)	68 (38.64)	282 (37.11)	359 (41.12)	167 (38.57)
Tertiary	28 (23.53)	27 (11.16)	19 (12.18)	37 (29.37)	45 (16.42)	17 (9.66)	154 (20.26)	120 (13.75)	42 (9.7)
Unemployed	58 (48.74)	159 (65.70)	128 (82.05)	54 (42.86)	177 (64.60)	138 (78.41)	402 (52.89)	552 (63.23)	352 (81.29)
Marital status									
Single	21 (17.65)	30 (12.4)	12 (7.69)	24 (19.05)	30 (10.95)	19 (10.8)	113 (14.87)	107 (12.26)	38 (8.78)
Married	72 (60.5)	141 (58.26)	90 (57.69)	69 (54.76)	164 (59.85)	96 (54.55)	443 (58.29)	515 (58.99)	238 (54.97)
Others	26 (21.85)	71 (29.34)	54 (34.62)	33 (26.19)	80 (29.2)	61 (34.66)	204 (26.84)	251 (28.75)	157 (36.26)
Alcohol consumption (= yes)	91 (76.47)	178 (73.55)	100 (64.10)	84 (66.67)	205 (74.82)	111 (63.07)	580 (76.32)	643 (73.65)	277 (63.97)
Smoking exposure (= yes)	11 (9.24)	32 (13.22)	23 (14.74)	14 (11.11)	32 (11.68)	22 (12.50)	100 (13.16)	118 (13.52)	58 (13.39)
Physical activity status									
Low	35 (29.41)	95 (39.26)	94 (60.26)	50 (39.68)	125 (45.62)	97 (55.11)	274 (36.05)	406 (46.51)	243 (56.12)
Moderate	44 (36.97)	81 (33.47)	44 (28.21)	36 (28.57)	89 (32.48)	52 (29.55)	242 (31.84)	274 (31.39)	129 (29.79)
High	40 (33.61)	66 (27.27)	18 (11.54)	40 (31.75)	60 (21.9)	27 (15.34)	244 (32.11)	193 (22.11)	61 (14.09)
Health status burden									
No burden	30 (25.21)	15 (6.2)	0 (0)	22 (17.46)	22 (8.03)	5 (2.84)	132 (17.37)	69 (7.9)	6 (1.39)
Moderate burden	64 (53.78)	172 (71.07)	75 (48.08)	76 (60.32)	175 (63.87)	69 (39.2)	422 (55.53)	513 (58.76)	156 (36.03)
Severe burden	25 (21.01)	55 (22.73)	81 (51.92)	28 (22.22)	77 (28.1)	102 (57.95)	206 (27.11)	291 (33.33)	271 (62.59)
Disability status									
No disability	96 (80.67)	146 (60.33)	41 (26.28)	104 (82.54)	153 (55.84)	66 (37.50)	534 (70.26)	499 (57.16)	139 (32.10)
Moderate disability	9 (7.56)	59 (24.38)	56 (35.9)	10 (7.94)	84 (30.66)	64 (36.36)	118 (15.53)	232 (26.58)	159 (36.72)
Severe disability	14 (11.76)	37 (15.29)	59 (37.82)	12 (9.52)	37 (13.5)	46 (26.14)	108 (14.21)	142 (16.27)	135 (31.18)
Healthcare utilisation (= yes)	39 (32.77)	175 (72.31)	152 (97.44)	47 (37.30)	209 (76.28)	170 (96.59)	108 (9.88)	565 (51.69)	420 (38.43)
Life satisfaction with-									
Employment, mean (sd)	4.82 (3.89)	3.47 (3.9)	1.96 (3.43)	4.48 (3.97)	3.39 (3.97)	1.64 (3.12)	4.08 (4.04)	3.52 (3.95)	1.92 (3.43)
Financial situation, mean (sd)	7.39 (1.98)	6.5 (2.53)	5.99 (2.57)	7.33 (2.01)	6.76 (2.31)	6.32 (2.65)	7.14 (2.17)	6.64 (2.43)	6.13 (2.6)
Social supports, mean (sd)	7.94 (1.68)	7.67 (2.17)	7.74 (1.95)	7.82 (1.74)	7.92 (1.71)	7.44 (2.1)	8 (1.62)	7.78 (1.91)	7.63 (2.02)
Remoteness									
Major Cities	79 (66.39)	151 (62.4)	105 (67.31)	91 (72.22)	151 (55.11)	103 (58.52)	488 (64.21)	505 (57.85)	271 (62.59)
Inner Regional	27 (22.69)	55 (22.73)	35 (22.44)	26 (20.63)	87 (31.75)	50 (28.41)	175 (23.03)	235 (26.92)	109 (25.17)
Outer Regional	11 (9.24)	32 (13.22)	16 (10.26)	6 (4.76)	28 (10.22)	20 (11.36)	80 (10.53)	119 (13.63)	48 (11.09)
Remote or very remote	2 (1.68)	4 (1.65)	0 (0)	3 (2.38)	8 (2.92)	3 (1.7)	17 (2.24)	14 (1.6)	5 (1.15)
Socioeconomic status									
Q_1 (lowest 20%) (ref)	17 (14.29)	50 (20.66)	48 (30.77)	18 (14.29)	41 (14.96)	45 (25.57)	127 (16.71)	160 (18.33)	120 (27.71)

(*Continued*)

Table 2. (Continued)

Variables	Wave-13			Wave-17			Overall		
	Number of chronic comorbid conditions, n (%)			Number of chronic comorbid conditions, n (%)			Number of chronic comorbid conditions, n(%		
	0	1–2	3 or more	0	1–2	3 or more	0	1–2	3 or more
Q_2	22 (18.49)	59 (24.38)	38 (24.36)	22 (17.46)	62 (22.63)	48 (27.27)	147 (19.34)	208 (23.83)	115 (26.56)
Q_3	21 (17.65)	29 (11.98)	27 (17.31)	21 (16.67)	51 (18.61)	30 (17.05)	146 (19.21)	152 (17.41)	71 (16.40)
Q_4	32 (26.89)	51 (21.07)	23 (14.74)	27 (21.43)	64 (23.36)	25 (14.20)	177 (23.29)	182 (20.85)	69 (15.94)
Q_5 *(highest 20%)*	27 (22.69)	53 (21.9)	20 (12.82)	38 (30.16)	56 (20.44)	28 (15.91)	163 (21.45)	171 (19.59)	58 (13.39)
Overall	119 (23.02)	242 (46.81)	156 (30.17)	126 (21.88)	274 (47.57)	176 (30.56)	760 (36.79)	873 (42.26)	433 (20.96)

Na = not available

https://doi.org/10.1371/journal.pone.0228744.t002

of their physical ability [60,73]. Several reasons might influence this reduction in their physical strength. For example, a course of advanced cancer treatment is associated with considerable physical and psychological side effects in elderly cancer patients (e.g., weight change, muscle loss, fatigue, and physical weakness) [74], and exposure to multiple comorbidities [64,65,75] will presumably contribute to worse health status. Although, cancer patients in older age groups are less likely to be offered cancer treatments (e.g., chemotherapy, radiotherapy and axillary lymph node dissection) that may then contribute to a greater burden of health [74]. This result indicates that rehabilitation-related interventions (e.g., physical therapies) are essential to prevent or alleviate chronic comorbid conditions and an emerging cancer research area, particularly focused on the elderly [76].

The present study found that cancer patients who performed lower levels of physical activities were strongly associated with an extreme level of chronic comorbidities compared with patients engaged in high-level physical activity. This finding is in line with other studies [52,77,78], whereby it was found that limited physical activity levels were significantly associated with a higher risk of having chronic comorbid conditions in cancer patients. The magnitude of limited physical activity level may decrease the risk for several cancers by some mechanisms, including decreasing sex hormones, metabolic hormones and inflammation, and improving immune function [77]. In terms of cancer risk, high levels of physical activities (compared with low levels) played a significant role in the prevention of several cancers (e.g., 42% for gastrointestinal cancer, 23% for renal cancer, and 20% for myeloid leukemia) [79].

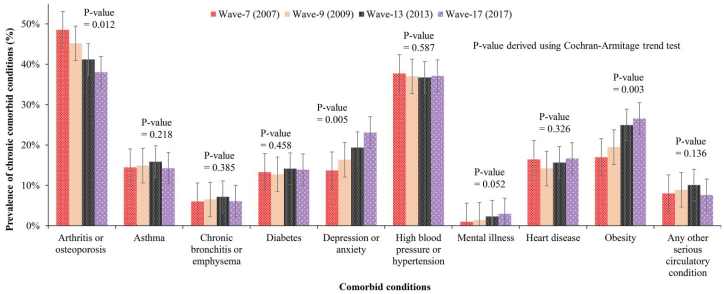

Fig 2. The trend of disease pattern among patients with cancer.

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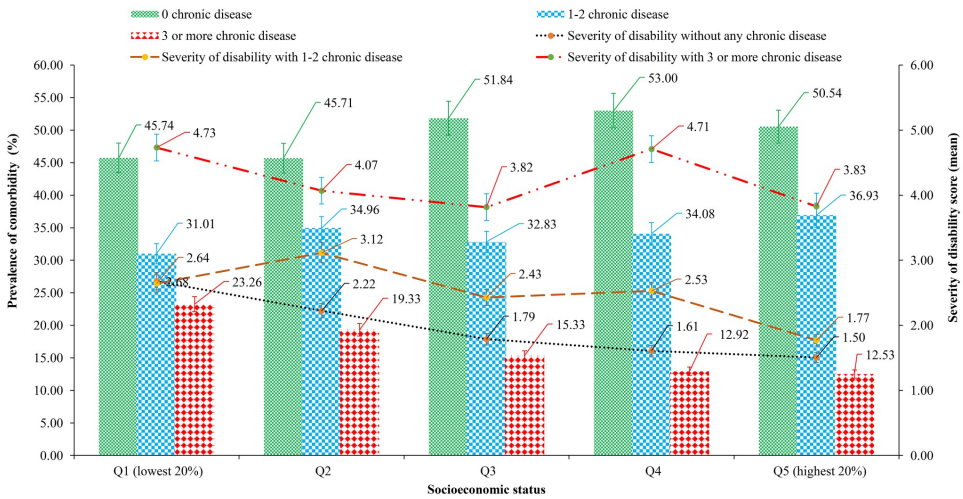

Fig 3. Unequal distribution of the presence of chronic comorbidities with the severity of disability among cancer patients across socioeconomic status.

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This includes averting genetic damage, improving the immune system, reducing chronic infections, and controlling cancer cells [79]. In addition, some past studies confirmed that physical activity plays an effective role in controlling the side effects of cancer treatment and disease progression, reducing psychological conditions [77,80] and reducing the risk of developing future cancers [81]. Several hypotheses and mechanisms have been suggested regarding the anti-cancer effects of physical activities. The American Cancer Society guidelines for cancer survivors [82] recommend daily physical activities, including a continuation of normal daily life activities immediately after diagnosis, which help to significantly reduce physical stamina and muscle strength erosion as well as anxiety levels, thereby resulting in the prevention of long-term adverse health outcomes (e.g., extreme comorbidity burden and disability) [83]. In this context, future research could examine the influence that physical activity has on the effectiveness of chronic comorbid conditions among cancer patients.

The risks of having extreme chronic comorbidity conditions amongst cancer patients who lived in the poorest households were more pronounced compared with their richer counterparts. Recent studies confirm this result with the disadvantaged socioeconomic status of cancer survivors being negatively associated with long-term adverse health outcomes (e.g., multiple chronic illnesses, physical disability) [83–93]. Some studies also provided evidence that the magnitude of the cancer burden is adversely associated with socioeconomic status [16, 32–35]. Further, adverse cancer outcomes (e.g., worse health status and long-term chronic illness) were disproportionately found in poorer people as opposed to those of higher socioeconomic status [13, 16, 32, 34]. Some reasons that have contributed to the high rates of long term health impacts among the poorest groups include higher tobacco consumption [16,28], economic burden [36,37], increased mental illness [94], lack of health education and awareness [95], and less access to competent and effective health care services [95]. Low productivity, loss/reduction of household income, and increased healthcare expenditure are more pronounced amongst the poorest cancer patients. Growing socioeconomic disparities of cancer outcomes need the

Table 3. Factors influencing chronic comorbid conditions of cancer patients using a fixed-effect negative binomial regression model.

Variables	Unadjusted model[1]		Adjusted model[2]	
	IRR (SE)	95% CI	IRR (SE)	95% CI
Female (ref = male)	1.04 (0.05)	(0.94, 1.14)	-	-
Age group				
< 25 years (= ref)	1.00	-	1.00	-
25–45 years	0.72 (0.13)	(0.51, 1.03)	0.85 (0.14)	(0.61, 1.18)
46–65 years	1.15 (0.19)	(0.83, 1.58)	1.07 (0.16)	(0.79, 1.45)
>65 years	1.49*** (0.24)	(1.09, 2.04)	1.15** (0.17)	(1.08, 1.45)
Educational attainment				
Year 11 or below	1.48*** (0.12)	(1.26, 1.74)	1.16** (0.09)	(1.01, 1.35)
Year 12	1.11 (0.13)	(0.88, 1.40)	1.13 (0.12)	(0.91, 1.40)
Trade/certificate/diploma	1.38*** (0.12)	(1.17, 1.63)	1.21*** (0.09)	(1.05, 1.40)
Tertiary (= ref)	1.00	-	1.00	-
Unemployed (ref = employed)	1.80*** (0.10)	(1.62, 2.00)	1.08 (0.07)	(0.95, 1.23)
Marital status				
Single (= ref)	1.00	-	1.00	-
Married	1.21** (0.10)	(1.02, 1.42)	1.02 (0.08)	(0.87, 1.20)
Others	1.41*** (0.12)	(1.19, 1.68)	1.06 (0.09)	(0.90, 1.25)
Physical activity status				
Low	1.60*** (0.12)	(1.39, 1.85)	1.25** (0.07)	(1.09, 1.59)
Moderate	1.30*** (0.10)	(1.12, 1.52)	1.06 (0.07)	(0.92, 1.21)
High (= ref)	1.00	-	1.00	-
Alcohol consumption (ref = yes)	1.26*** (0.06)	(1.14, 1.39)	0.91 (0.05)	(0.82, 1.00)
Smoking exposure (ref = no)	1.02 (0.07)	(0.88, 1.18)	-	-
Healthcare utilisation (ref = no)	0.27 (0.02)	(0.24, 0.31)	0.38*** (0.03)	(0.33, 0.45)
Health status burden				
No burden (= ref)	1.00	-	1.00	-
Moderate burden	2.44*** (0.27)	(1.96, 3.03)	1.90*** (0.26)	(1.45, 2.48)
Severe burden	4.18*** (0.47)	(3.36, 5.21)	2.30*** (0.33)	(1.73, 3.05)
Disability status				
No disability (= ref)	1.00	-	1.00	-
Moderate disability	1.82*** (0.10)	(1.64, 2.02)	1.22*** (0.07)	(1.10, 1.36)
Severe disability	1.99*** (0.12)	(1.76, 2.24)	1.25*** (0.08)	(1.11, 1.41)
Life satisfaction with-				
Employment	0.94*** (0.01)	(0.92, 0.95)	0.98*** (0.01)	(0.97, 0.99)
Financial situation	0.97** (0.01)	(0.95, 0.99)	0.96*** (0.01)	(0.94, 0.98)
Social supports	0.96*** (0.01)	(0.93, 0.98)	1.03** (0.01)	(1.01, 1.05)
Remoteness				
Major cities (= ref)	1.00	-	-	-
Inner regional	1.02 (0.06)	(0.91, 1.14)	-	-
Outer regional	1.04 (0.08)	(0.90, 1.21)	-	-
Remote or very remote	0.77 (0.14)	(0.54, 1.11)	-	-
Socioeconomic status				
Q_1 (lowest 20%)	1.51*** (0.12)	(1.29, 1.77)	1.21*** (0.08)	(1.11, 1.29)
Q_2	1.35*** (0.11)	(1.15, 1.57)	1.09 (0.08)	(0.95, 1.26)
Q_3	1.19** (0.10)	(1.01, 1.41)	1.15 (0.09)	(0.99, 1.34)
Q_4	1.08 (0.09)	(0.92, 1.27)	0.99 (0.08)	(0.85, 1.15)

(*Continued*)

Table 3. (Continued)

Variables	Unadjusted model[1]		Adjusted model[2]	
	IRR (SE)	95% CI	IRR (SE)	95% CI
Q_5 (highest 20%) (= ref)	1.00	-	1.00	-

Note:

*p<0.05,

**p<0.01,

***p<0.001,

IRR = incidence rate ratio, *SE* = standard error, *CI* = confidence interval,

[1]Single explanatory variable was included in un-adjusted model,

[2]Explanatory variables were included in the adjusted model only if any label of the variable was significant at 5% or less risk level in the unadjusted model

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attention of governments, health systems, and decision-makers. For example, Cancer Council Australia has an optimal care pathway project, which has already addressed several cancer sites in disadvantaged areas. Such initiatives might help to reduce socio-economic disparities, which are related to poverty, gender, education, and health, and they should promote universal access to health care which can further enhance both socio-economic and human development.

This study has some limitations. Study participants were accessed from the *HILDA* survey, which covers health, economic, employment, income and health characteristics of household members aged 15 years and older. Children who suffered from cancer were excluded from this study. The study findings established a relationship between cancer diagnosis and chronic comorbidity conditions among cancer survivors, which might vary in terms of cancer stages and types of cancer. The authors were not able to estimate the cancer type analysis due to the paucity of relevant data. Further, the study findings were based on self-reported responses that might have been impacted by respondents' prejudice (e.g., silence and over-response), and by problems in understanding and interpreting the survey questions.

Despite these limitations, this study has some strengths including the use of a prospective longitudinal design of long term follow-ups and the application of well-validated and reliable longitudinal wave measures of the impacts of a cancer diagnosis on the burden of chronic comorbid conditions of individuals over the 2007–2017 period. The study population captured different dimensions including ethnically, geographically, and socio-economically diverse groups. Furthermore, this study included several potential confounding factors such as health status burden, the severity of the disability level as well as life satisfaction (e.g., employment, financial situation and, social supports) that were not present in previous studies. For this study, data were gathered from four-wave of the *HILDA* survey for cancer survivors. The length of the survey period may have introduced uncontrolled bias, as changes in health status are not instantaneous and might emerge only after time, which was not captured in this study. Due to the paucity of funding, the authors were unable to consider cancer patients who registered for cancer surveillance as well as received health care from other health facilities (e.g., private clinics, community clinics and, secondary or tertiary hospitals). Future study is required using a similar study design, perspective, and analytical methods in terms of cancer-specific exploration.

Conclusions

This study has shown an extreme burden of chronic comorbid conditions among cancer patients in Australia. Older patients, inadequate level of physical activities, the magnitude of health burden, and patients living in the poorest households were significant predictors associated with a higher risk of having chronic comorbidity conditions. The findings have further

implications for improving public health policy and reducing population-level unhealthy lifestyles, which should be recommended. The study results could be used to better outline the management of a sequelae course of treatment for those who should undergo more intensive physical rehabilitation aimed at reducing the risk of adverse health outcomes. Given the clinical significance of comorbidity in cancer survivors, this study may play a significant role in providing comprehensive evidence for health care providers, including physical therapists and oncologists, who should be aware of the unique problems that challenge this population and who should advocate for prevention and evidence-based interventions. Finally, a greater awareness of the importance of managing a patients overall health status within the context of comorbidity is warranted together with emphasised research on comorbidity to generate an appropriate scientific basis on which to build evidence-based care guidelines for these chronic comorbid conditions patients.

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2.4 Study 4

Cancer burden: Impact of long-term productivity related work disability and consequences

The *third study* of this thesis investigated the long-term chronic comorbid conditions in terms of disease pattern along with potential predictors among cancer patients and consequences over an extended period. *Study 4* captured the long-term impact of productivity-related work disability among cancer patients and consequences over an extended period.

Article IV: The changing relationship between health burden and work disability of Australian cancer survivors, 2003-2017: Evidence from a longitudinal survey

Study 4 aimed to examine the impact of health burden on the magnitude of work disability of cancer survivors in Australia over an extended period of 2003-2017. This study found that the prevalence of long-term disability among cancer survivors was 50%, while 18% of patients had experienced extreme work disability. The magnitude of disability levels has increased significantly with the level of health burden. Cancer survivors who faced a severe health burden were significantly higher risk of having work disability compared with patients who had no health burden. Other potential predictors, such as older patients, those engaged in lower levels of physical activities, those who drink alcohol, and poor socioeconomic status were all significantly associated with extreme work disability. This study concluded that a substantial proportion of cancer survivors experienced work disability that was more pronounced with the magnitude of health burden.

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The changing relationship between health burden and work disability of Australian cancer survivors, 2003–2017: evidence from a longitudinal survey

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Abstract

Background: The purpose of this study was to examine the relationship between the cancer health burden and themagnitude of work disability on cancer survivors in Australia from 2003 to 2017.

Methods: A longitudinal prospective study design was undertaken among cancer patients using data from the Household, Income and Labour Dynamics in Australia survey. The longitudinal effect was captured using a fixed effect multinomial logistic regression model, which predicted changes in the relationship between cancer burden and work disability level controlling for socio-demographic, lifestyle and life conditions predictors.

Results: The prevalence of long-term disability among cancer survivors was 50%, with 18% of patients experiencing extreme work disability. The magnitude of disability levels increased significantly with the level of health burden. Cancer survivors who faced a severe health burden were at 5.32 times significantly higher risk of having work disability compared with patients who had no health burden. Other potential predictors, such as older patients (relative risk ratio, RRR = 1.82; 95% CI: 1.57, 5.87), those engaged in lower levels of physical activities (RRR = 1.91; 95% CI: 1.07, 3.40), those who drink alcohol (RRR = 1.29; 95% CI: 1.15, 1.49), and poor socioeconomic status (RRR = 1.28; 95% CI: 1.16, 2.23) were all significantly associated with extreme work disability.

Conclusion: A substantial proportion of cancer survivors experienced work disability which was more pronounced with the magnitude of the cancer health burden. The different dimensions of disability might be prevented by introducing cancer survivor-specific evidence-based interventions, and incorporating comprehensive social support. Recommendations to improve public health policy aimed at reducing population-level unhealthy lifestyle behaviours include: using these findings to better outline the management of a sequelae course of treatment for cancer survivors; and identifying those who should undergo more intensive physical rehabilitation aimed at reducing their work disability level.

Keywords: Australia, Cancer survivors, Health burden, Longitudinal prospective study, Work disability

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Background

Worldwide, work participation of cancer survivors has seen a surge of attention in the last two of decades [1]. A cancer diagnosis can be a devastating and, often,life-threatening experience [2], which frequently results in short- or long-term disability [3–6] due to both health and economic burdens [7]. Cancer imposes a substantial burden in terms of reducing the autonomy of individuals to perform their general daily activities [1, 8]. Furthermore, a cancer diagnosis negatively affects employment status in terms of job opportunities, work participation and work ability due to the illness [1, 8]. The adverse side-effects of treatment results in physical and psychological limitations that can be a barrier to work participation [9]. However, the burden of physical disability levels varies by cancer stages and types [10]. Cancer survivors run a significantly high risk of unemployment and early retirement, and they have less opportunity to be re-employed [1]. A cohort study showed that 20% of cancer survivors reported disabilities due to cancer over a 5 year follow-up period [11]. An estimated 30% of cancer survivors reported work disabilities post-treatment [12]. However, a prospective cohort study confirmed that the employment opportunities of cancer survivors were adversely impacted by their recovery and health status [13]. Return to work participation may assist cancer survivors to recover faster, improve their quality of life, help return them to their former 'normal' life, increase their self-confidence, and may support them to overcome the negative side-effects of treatment [14, 15]. Furthermore, improvement of work participation of cancer survivors contributes to societal benefit, by reducing absenteeism, and reducing disability benefit payments and productivity losses [16]. Notably, cancer survivors' earnings are 10% lower compared to non-cancer survivors [17]. Therefore, there is a greater need to provide supportive services (e.g., related to rehabilitation) to both help cancer survivors adapt to disability, and prevent work disability in this patient population.

In Australia, the incidence of cancer in individuals results in different disability levels for cancer survivors [2]. The long-term effects of cancer treatment are a significant cause of greater absenteeism, higher unemployment and early retirement [18], and overall reduced participation in work [2–6]. Approximately 40% of Australian cancer patients are of working age [19], with 46% being unable to return to employment after a cancer diagnosis [20], and 67% changing their employment status following diagnosed [21]. This results in a reduction of $1.7 billion to Australian gross domestic product (GDP) annually [20]. The impact of work disability constitute a substantial burden for people who have not had an occupation due to cancer, as well as to their families and employers. Furthermore, cancer-related treatment results in patients experiencing economic burden due to high out-of-pocket expenses (e.g., medicines and advanced treatments, including diagnostics), lost productivity, loss/reduction of household income, and other induced expenditure [22]. The majority of cancer patients depend on family, relatives and friends for physical and economic support during their course of treatment and in the last stages of the disease [23, 24]. Ultimately, cancer survivors are faced with a double burden in terms of their health and economic situation.

Existing studies have focused on cancer survivors' characteristics and work participation, including in the United States [1, 10, 12, 16, 25–27], Canada [3, 13], South Korea [8], the Netherlands [5, 6, 9], and Belgium [4, 28]. A number of factors adversely influencing work participation of patients with cancer has been determined in different settings. These parameters are associated with patients' socio-demographic characteristics (e.g., age, educational status and economic position) [5, 6, 9, 27], disease-related factors (e.g., tumor site, advanced tumor stage), advanced course of treatment (e.g., chemotherapy) [3, 6, 7, 27], and work-related factors (e.g., physical work demands) [1, 9]. The presence of comorbid conditions in cancer patients creates a higher likelihood of work-related disability [3]. That is, cancer survivors with poor health status were significantly correlated with a higher level of work disability [27]. A study conducted in the Netherlands found that cancer survivors who had experienced hormone therapy, metastatic disease, had limited physical strength, and limited workability, were strongly and adversely associated with a higher risk of work disability [5, 6]. The poor perceptions of cancer survivors, in terms of their health and work ability [6], their unhealthy behaviours (e.g., alcohol consumption), and their clinical stage [29] were also significant predictors in determining independent effects of their work disability levels.

In Australia, studies have been conducted among cancer patients exploring the psychological effects of current treatment or level of disability [30], association with work-related stress and cancer [31], and lost productivity due to cancer [20]. However, very limited evidence exists of the health burden in relation to work disability of cancer survivors in Australia. That is, potential factors associated with work disability of cancer survivors are poorly explored. This may be partially accounted for by various study designs, analytical rigour and follow-up periods. For instance, many international studies have used a limited number of predictors. The majority of the previous studies have been cross-sectional in nature, in terms of clinical and treatment perspectives. Thus, a comprehensive study is important to examine the impact of the health burden in relation to the magnitude of work disability as a long-term sequela of patients with cancer. There has been a

recent surge of attention in the field of cancer survivorship, leading to efforts to identify and manage treatment-related sequelae, enhance quality of life, and improve the overall functioning of people who are receiving long-term follow-up care after cancer treatment.

Using longitudinal data from nationally representative Australian samples, these findings will help to improve the understanding of potential employment opportunities after a cancer diagnosis. In addition, these findings may be considered from different perspectives in cancer policy discussions: the cancer survivor (e.g., health status, work disability level, return to employment); the caregiver and the family (e.g., the health burden, reduction of socio-economic position, risk of poverty); the employer and co-workers (e.g., employment conditions, workload); the health care provider (e.g., supportive care needs, effective programs and interventions); and the community or society (e.g., economic and policy changes).

The present study aims to examine the health burden impact on the magnitude of work disability of cancer survivors after controlling several factors (e.g., socioeconomic, lifestyle, healthcare utilisation, and geographical location) over an extended period of 2003–2017. To achieve the research aim, the following three research questions (RQ) were posed:

RQ-1: What is the magnitude of work disability levels among cancer patients in Australia?

RQ-2: What is the longitudinal association between health burden and the magnitude of work disability among cancer patients in Australia over 2003–2017?

RQ-3: What are the potential predictors associated with the magnitude of work disability for cancer patients in Australia over this extended period?

Methods

Setting and data source

The study was conducted in the context of Australia. The Household, Income and Labour Dynamics in Australia (HILDA) study is a nationally representative household-based panel study. Data were collected from Australia residents aged 15 or over through face-to-face interviews and questionnaires, followed by re-interviews with the people in subsequent years. The details of the methods of data collection, including the sampling technique, have been reported elsewhere [32]. The overall goal of HILDA study is to collect data on the lives of Australian residents in terms of wealth, retirement, fertility, health, education, skills and abilities. Households and individuals are interviewed every year, allowing researchers to see how participants'lives change over time. Household longitudinal data, known as panel data, provides a more complete picture than cross-sectional data as it documents the life course each person takes. In many cases, panel data allows causal inferences that are more credible than those elicitedfrom other types of data. In particular, statistical methods known as 'fixed-effects' regression models can be employed to examine the effects of various factors on life outcomes such as long-term health conditions, earnings, unemployment, income and life satisfaction. These models can control for the effects of stable characteristics of individuals that are typically not observed, such as innate ability, motivation and optimism, that confound estimates of causal effects in cross-sectional settings.

Study participants

The study was a sub-study with participants selected based on inclusion criteria of the HILDAsurvey [32], namely: 1) population aged 15 years or more (as per HILDA study participants), ii) diagnosed cancer patients, iii) longitudinal household members, and iv) willing to participate in HILDA study. The study participants were patients with cancer and data were derived from HILDA waves 3, 7, 9, 13 and 17, all of which had a health focus and asked specific questions related to cancer. Other survey waves were excluded from this study due to the paucity of cancer related information. A total of 2571 patients with diagnosed cancer were potential study participants (Fig. 1) from the five waves (505 patients from wave-3 in 2003, 557 patients from wave-7 in 2007, 416 patients from wave-9 in 2009, 517 patients from wave-13 in 2013 and 576 patients from wave-17 in 2017).

Study design

The present study design was a mixed-longitudinal quantitative design in patients with cancer. Individuals who experienced a cancer diagnosis were examined with a focus on the magnitude of the cancer burden associated with their long-term-disability. To examine the mixed-longitudinal effects, this study hypothesised that several factors related to individuals' socio-demographic characteristics, social factors, and disease-related symptomatic factors might influence outcome factors like disability. The combination of factors was expected to predict the patients' long-term disability or adverse occurrence.

Study variables

Outcome variable

Disability status and severity of disability were considered outcome measures. Work disability was measured by asking participants if they had any long-term health condition, impairment or disability that limited the kind or amount of work they could do. The magnitude of disability level was measured based on patients' responses

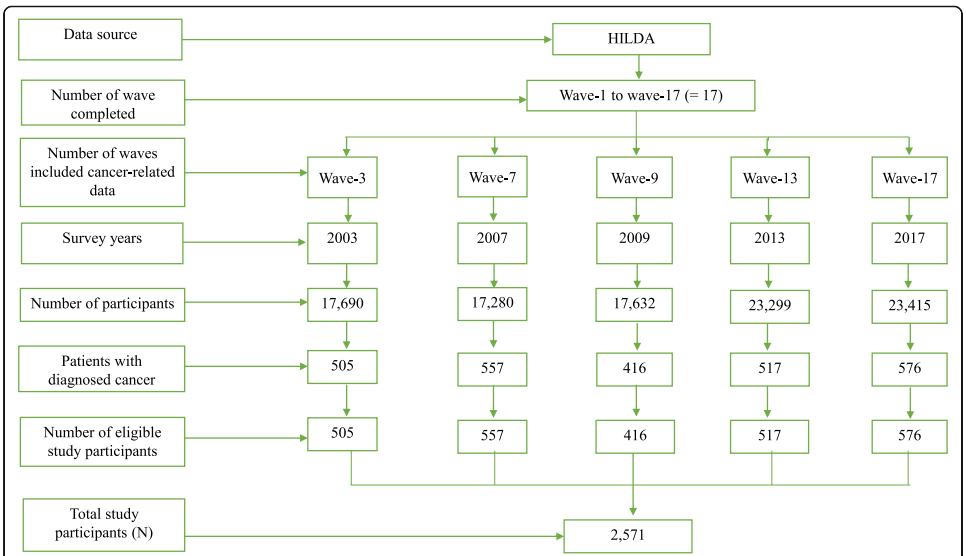

Fig. 1 Distribution of study participants

as "Could you pick a number between 0 and 10 to indicate how much your condition [s] limit [s] the amount of work you can do?" The severity of disability score was ranged from 0 to 10, with 10 indicating 'able to do any work' and 0 indicating 'not at all'. The severity of disability level was defined as follows: (i) 'no disability' if disability score was equal to zero, (ii) 'moderate disability' for disability scores of 1 to 6, and (iii) 'severe disability' for disability scores of 7 to 10. The levels of disability were considered dependent variables in the analytical model.

Explanatory variables

This study considered several demographic, socio-economic and health and lifestyle-related variables as predictors of long-term disability. The demographic variables included participant's gender (male or female); age (< 25 years, 25–45 years, 46–65 years, or > 65 years), educational background (up to year 11, year 12, trade/certificate/diploma, or tertiary education), employment status (employed or unemployed), marital status (single, married, other including separated, divorced or widowed), and household size (< 3 members, 3 to 4 members, 5 or more members). Ethnic status was defined as Aboriginal or non-Aboriginal. Lifestyle factors include physical activity status (low, moderate, or high). Life condition-related variables such as satisfaction with household members, overall employment situation, financial situation and social supports were also considered as potential predictors. The level of satisfaction-related variables ranged from 0 (totally dissatisfied) to 10 (totally satisfied). Private insurance coverage of patients was dichotomous (insured or uninsured). Medication status was defined as 'with medication' or 'without medication'.

To measure the impact upon quality of life the short form (SF)-36 was used. Health burden levels were defined as follows: (1) high burden if SF-36 score was less than 50, (2) moderate burden if SF-36 score was greater than or equal to 50 but less than 90, (3) no burden if SF-36 score was greater than or equal to 90 [33]. Remote locations were defined according to the accessibility to services and the Remoteness Index of Australia [34], and they were classified into five groups: major cities, inner regional, outer regional and remote or very remote. The index of relative socio-economic disadvantage (IRSD) was used to measure socio-economic status (SES). T This is a geographical area-based estimate of socio-economic status using a combination of income, education level and occupation where communities are ranked and categorised from economically disadvantaged to wealthy.he cut-off values for each of the quintiles are as follows: Q_1 (IRSD ≤927.0), Q_2 (927.0 > IRSD ≤965.8), Q_3 (965.8 > IRSD ≤1001.8), Q_4 (1001.8 > IRSD ≤1056.0), or Q_5 (IRSD > 1056.0) [35].

Statistical analysis

The overall cohort, and the subgroup that dropped out over the course of study, were characterized using frequency, means and proportions to summarise the participants' characteristics in terms of demographics, unhealthy behaviours, life satisfaction, healthcare utilisation, remoteness and socioeconomic status. The association between the level of disability or disability status and the variables of greatest interest was analysed using the chi-square test or one way analysis of variance (ANOVA) where appropriate. During the analytical exploration, the present study also considered the missing data mechanisms as suggested by Rubin et al. (1976) and Little and Rubin (2002) [36, 37]. They classified the missing data process into three mechanisms: missing completely at random (MCAR), missing at random (MAR), and non-ignorable missing (NIM). In the study of work disability among cancer patients over time, missing data are closed to MCAR if the probability of attrition does not depend on the presence or severity of work disability (i.e., no disability, moderate disability or severe disability). A fixed-effects multinomial logistic regression model was used for analysis under the assumption of MCAR.

Both unadjusted and adjusted fixed-effect multinomial logistic regression models were used to identify the potential factors that had a significant role in the severity of disability level. In the regression model, the dependent variable (the severity of disability) was characterised by a categorical variable with three different levels (no disability, moderate disability or severe disability). The model was tested for sensitivity by the forward selection procedure (e.g., including and excluding specific variables) with the robust standard error. The predictor variables were included in the adjusted model only if any label of the predictor was significant at ≤5% risk level in the unadjusted regression model, which in turn was used to adjust for the effects of other potential confounders. Insignificant predictors were not included in the adjusted model. For independent variables, the category found to be least at risk of having an extreme or moderate disability level in the analysis was considered as the reference for constructing relative risk ratio (RRR), using fixed-effect multinomial logistic regression. During the data analysis, the study also looked at interaction effects in the analytical exploration, the interaction effects of the magnitude of long-term work disability in relation to RQ-3 by examining: age, employment status, life satisfactions, unhealthy behaviors and socio-economic status. We did not include the interaction effects in the results section and tables because the effects were insignificant in unadjusted model at a borderline risk level ($P = 0.125$). All data analyses were undertaken using the statistical software Stata/SE 13 (StataCorp, College Station, TX, USA). The statistical significance was considered at a 5% risk level.

Results

Description of study participants

Data from 2571 cancer patients were included in the analysis (Table 1). The percentage of male participants (54%) was higher than the female (46%). Approximately 45% of patients were senior, aged (> 65 years), followed by middle-aged (38%) (46 to 65 years). Approximately 47% had a middle or high school level education, with 15% of cancer patients having tertiary educationl qualifications. Approximately 45% of patients had limited exposure to physical activity, and only 23% of patients experienced high-level physical activities each week. Two-thirds of participants drank alcohol frequently. The majority of participants (90%) reported a moderate or high health burden in terms of their quality of life. In addition, 56% were insured, 72% received prescribed medication, and 60% lived in major cities.

Distribution of disability status among cancer patients (for RQ 1)

Table 2 shows participants' characteristics, overall and by disability status, across the selected variables. Half of the male patients experienced a long-term disability. The prevalence of disability increased significantly ($P < 0.001$) as patients aged (e.g., 17% for below 25 years, 27% for 25–45 years, 42% for 46–65 years, 66% for more than 65 years old). Approximately 58% of patients who had completed a middle or high school education level lived with a disability, followed by 48% of tertiary educated patients. The prevalence of disability was pronounced amongst the unemployed (65%), those who were poorly engaged in physical activities (61%) and those who were uninsured (59%). Furthermore, the proportion of disability was significantly aligned with the magnitude of cancer burden (e.g., 71% for severe burden, 45% for moderate burden and 23% for no burden). Regarding socio-economic status, the magnitude of work disability was found to be highest in the lowest socio-economic quintile. For example, patients who lived in the poorest households (23%) were significantly exposed to long-term disability ($P < 0.001$) compared with those in the richest households (16%). However, an upward trend in work disability levels was observed among the poorest cancer survivors during 2003–2017 (Fig. 2).

Association between severity of disability and patient's characteristics (for RQ 2)

The age distribution of patients contributed significantly ($P < 0.001$) to the magnitude of long-term disability (Table 2). Educational background was significantly associated with disability level ($P < 0.001$). Several patient

Table 1 Characteristics of cancer patients by disability status

Variables	n (%) / n (mean)	Disability distribution among cancer survivors		*P*-value
		Any disability, n (%)	No disability, n (%)	
Sex				
Male	1398 (54.38)	711 (50.86)	687 (49.14)	0.353
Female	1173 (45.62)	575 (49.02)	598 (50.98)	
Age				
< 25 years	63 (2.45)	11 (17.46)	52 (82.54)	< 0.001
25–45 years	383 (14.90)	103 (26.89)	280 (73.11)	
46–65 years	975 (37.92)	409 (41.95)	566 (58.05)	
> 65 years	1150 (44.73)	763 (66.35)	387 (33.65)	
Educational attainment				
Year 12 or below	989 (38.47)	573 (57.94)	416 (42.06)	< 0.001
Year 12	220 (8.56)	97 (44.09)	123 (55.91)	
Trade/certificate/diploma	977 (38.00)	468 (47.90)	509 (52.10)	
Tertiary	385 (14.97)	148 (38.44)	237 (61.56)	
Employment status				
Employed	974 (37.88)	247 (25.36)	727 (74.64)	< 0.001
Unemployed	1597 (62.12)	1039 (65.06)	558 (34.94)	
Physical activity status				
Low	496 (45.38)	301 (60.69)	195 (39.31)	< 0.001
Moderate	346 (31.66)	176 (50.87)	170 (49.13)	
High	251 (22.96)	99 (39.44)	152 (60.56)	
Alcohol consumption (= yes)	1903 (74.02)	887 (46.61)	1016 (53.39)	< 0.001
Smoking exposure (= yes)	370 (14.39)	179 (48.38)	191 (51.62)	0.095
Health burden				
No burden	257 (10.00)	59 (22.96)	198 (77.04)	< 0.001
Moderate burden	1566 (60.91)	698 (44.57)	868 (55.43)	
Severe burden	748 (29.09)	529 (70.72)	219 (29.28)	
Private insurance coverage				
Yes	613 (56.08)	292 (47.63)	321 (52.37)	< 0.001
No	480 (43.92)	284 (59.17)	196 (40.83)	
Healthcare utilisation				
Yes	1093 (72.43)	682 (62.40)	411 (37.60)	< 0.001
No	416 (27.57)	115 (27.64)	301 (72.36)	
Life satisfaction with (mean scores)				
Household members	2571 (8.20)	8.23 (1.85)	8.17 (1.83)	0.786
Employment	2571 (3.37)	2.29 (3.62)	4.45 (3.98)	< 0.001
Financial situation	2571 (6.72)	6.54 (2.49)	6.89 (2.29)	0.005
Social supports	2571 (7.91)	7.79 (1.89)	8.03 (1.73)	< 0.001
Remoteness				
Major cities	1552 (60.37)	774 (49.87)	778 (50.13)	< 0.001
Inner regional	660 (25.67)	336 (50.91)	324 (49.09)	
Outer regional	314 (12.21)	158 (50.32)	156 (49.68)	
Remote or very remote	45 (1.75)	18 (40.00)	27 (60.00)	
Socioeconomic status				

Table 1 Characteristics of cancer patients by disability status *(Continued)*

Variables	n (%) / n (mean)	Disability distribution among cancer survivors		*P*-value
		Any disability, n (%)	No disability, n (%)	
Q_1 *(lowest 20%) (ref)*	516 (20.07)	293 (22.78)	223 (17.35)	< 0.001
Q_2	595 (23.14)	322 (25.04)	273 (21.25)	
Q_3	463 (18.01)	225 (17.50)	238 (18.52)	
Q_4	534 (20.77)	238 (18.51)	296 (23.04)	
Q_5 *(highest 20%)*	463 (18.01)	208 (16.17)	255 (19.84)	
Overall	2571 (100.00)	1286 (50.02)	1285 (49.98)	

characteristics including employment status ($P < 0.001$), insurance coverage ($P = 0.005$), utilisation of prescribed medication ($P < 0.001$), life satisfaction related-factors ($P < 0.05$), alcohol consumption ($P < 0.001$), geographical location ($P < 0.001$) and socio-economic status ($P < 0.001$) were significant predictors of disability level. Furthermore, the level of physical activity ($P < 0.001$) and the health burden related to cancer ($P < 0.001$) were dominant variables for the severity of the disability.

Factors influencing disability among patients with cancer (for RQ 3)

Table 3 shows the results of the fixed effect multinomial logistic regression analysis. In the final model, age, educational achievement, physical activities, health burden associated with cancer, utilisation of prescribed medication, patients living in a regional location, and those in the poorest households were significant predictors of a higher risk of long-term disability. An aged patient (> 65 years old) was at 1.82 times higher risk of having an extreme disability (RRR = 1.82; 95% CI: 1.57, 5.87) compared with a younger patient (< 25 years), while being 1.40 times more likely to have a moderate level of disability (RRR = 1.40; 95% CI: 1.09, 4.00). Patients who were unemployed had a significantly higher risk of being affected by severe disability (RRR = 2.01; 95% CI: 1.15, 3.50) or a moderate level of disability (RRR = 1.55; 95% CI: 1.01, 2.39) compared with their employed counterparts. Similarly, patients who performed a lower level of physical activities were 1.91 times more likely to have an extreme disability (RRR = 1.91; 95% CI: 1.07, 3.40) compared with patients engage in high-level physical activities. Patients who had an extreme health burden associated with cancer were at approximately five times significantly higher risk of experiencing a severe or moderate disability level compared with patients who reported excellent health status. Unhealthy behavioural factors like alcohol consumption (RRR = 1.29; 95% CI: 1.15, 1.49) were associated with work disability compared with patients who had not consumed alcohol. The risks of having an extreme disability (RRR = 1.28 times) or moderate disability level (RRR = 1.36 times) of cancer patients who lived in the poorest households were more pronounced compared with their richer counterparts.

Discussion

Cancer is significantly correlated with workdays lost and high levels of work-related disability [29, 38–40]. The main objectives of this study were to investigate the magnitude of work disability due to a cancer diagnosis and measure the longitudinal association between health burden and disability, and the potential predictors of work disability of cancer patients. The study results show that 50% of cancer patients experienced a long-term disability, whereas approximately 18% of patients had reached an extreme level of work disability. Furthermore, the prevalence of disability was pronounced in relation to the level of the cancer burden (e.g., 71% for severe burden, 45% for moderate burden, and 23% for no burden), aged patients (66%), and unemployed patients (65%), those engaged in limited physical activities (61%), the uninsured (59%), and the poorest socio-economic group (23%). Potential predictors, which included factors such as age, those who exercise less or not at all, those who have an extreme health burden, and engage in unhealthy behaviours (e.g., alcohol consumption), were significantly associated with a higher risk of having an extreme disability.

The results showed that a higher risk of a severe or moderate disability level was pronounced among cancer patients who faced an extreme health burden, compared with patients who reported an excellent health status. A previous study found that poor health status of cancer patients resulted in greater functional disability (e.g., specific task difficulties) [41, 42]. However, the prevalence of long-term disability was more pronounced in combination with a cancer diagnosis [5, 6, 12, 27, 29]. Advanced cancer treatments can damage healthy cells or organs [43]. For example, radiation and chemotherapy may impose short and long-term health problems and impact on the spinal cord, nerves and brain, which then may significantly contribute to long-term adverse outcomes like work-related disability. In the context of Australia, a significant proportion (46%) of cancer

Table 2 Association of severity of disability and characteristics of cancer patients

Variables	Severity of disability						
	No disability		Moderate disability		Severe disability		*P*-value
	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	
Sex							
Male	816	58.37 (55.76, 60.93)	335	23.96 (21.80, 26.27)	247	17.67 (15.76, 19.76)	0.728
Female	672	57.29 (54.43, 60.10)	297	25.32 (22.91, 27.89)	204	17.39 (15.33, 19.67)	
Age							
< 25 years	46	73.02 (60.69, 82.58)	9	14.29 (7.56, 25.35)	8	12.70 (6.44, 23.51)	< 0.001
25–45 years	285	74.41 (69.80, 78.54)	61	16.00 (12.59, 19.95)	37	9.66 (7.08, 13.06)	
46–65 years	606	62.15 (59.06, 65.15)	214	21.95 (19.46, 24.66)	155	15.90 (13.73, 18.33)	
> 65 years	551	47.91 (45.03, 50.81)	348	30.26 (27.67, 32.98)	251	21.83 (19.53, 24.31)	
Educational attainment							
Year 12 or below	489	49.44 (46.33, 52.56)	284	28.72 (25.98, 31.62)	216	21.84 (19.37, 24.53)	< 0.001
Year 12	147	66.82 (60.31, 72.74)	36	16.36 (12.03, 21.87)	37	16.82 (12.42, 22.37)	
Trade/certificate/diploma	588	60.18 (57.08, 63.21)	234	23.95 (21.38, 26.73)	155	15.86 (13.70, 18.29)	
Tertiary	264	68.57 (63.75, 73.02)	78	20.26 (16.53, 24.58)	43	11.17 (8.38, 14.73)	
Employment status							
Employed	740	75.98 (73.19, 78.56)	158	16.22 (14.04, 18.67)	76	7.80 (6.27, 9.66)	< 0.001
Unemployed	748	46.84 (44.40, 49.29)	474	29.68 (27.49, 31.97)	375	23.48 (21.47, 25.63)	
Physical activity status							
Low	233	46.98 (42.61, 51.39)	126	25.40 (21.76, 29.43)	137	27.62 (23.86, 31.73)	< 0.001
Moderate	197	56.94 (51.65, 62.07)	101	29.19 (24.63, 34.21)	48	13.87 (10.61, 17.94)	
High	176	70.12 (64.15, 75.47)	55	21.91 (17.21, 27.47)	20	7.97 (5.19, 12.04)	
Alcohol consumption (= yes)	1175	61.74 (59.54, 63.90)	448	23.54 (21.69, 25.50)	280	14.71 (13.19, 16.38)	< 0.001
Smoking exposure (= yes)	224	60.54 (55.46, 65.41)	82	22.16 (18.21, 26.69)	64	17.30 (13.77, 21.50)	0.455
Health burden							
No burden	248	96.50 (93.40, 98.17)	7	2.72 (1.30, 5.61)	2	0.78 (0.19, 3.07)	< 0.001
Moderate burden	1018	65.01 (62.61, 67.33)	403	25.73 (23.63, 27.96)	145	9.26 (7.92, 10.80)	
Severe burden	222	29.68 (26.51, 33.06)	222	29.68 (26.51, 33.06)	304	40.64 (37.17, 44.21)	
Private insurance coverage (= yes)	362	59.05 (55.10, 62.89)	155	25.29 (22.00, 28.89)	96	15.66 (12.99, 18.76)	0.005
Healthcare utilisation (= yes)	495	45.29 (42.35, 48.26)	340	31.00 (28.43, 33.92)	258	23.60 (21.18, 26.22)	< 0.001
Life satisfaction with (mean scores)							
Household members	1488	8.18 (8.09, 8.27)	632	8.24 (8.10, 8.38)	451	8.20 (8.01, 8.39)	0.034
Employment	1488	4.30 (4.10, 4.51)	632	2.48 (2.20, 2.77)	451	1.53 (1.25, 1.82)	< 0.001
Financial situation	1488	6.94 (6.83, 7.06)	632	6.59 (6.40, 6.78)	451	6.15 (5.91, 6.39)	< 0.001
Social supports	1488	8.01 (7.93, 8.09)	632	7.92 (7.78, 8.06)	451	7.61 (7.42, 7.80)	< 0.001
Remoteness							
Major cities	945	60.89 (58.43, 63.29)	347	22.36 (20.35, 24.50)	260	16.75 (14.97, 18.7)	< 0.001
Inner regional	344	52.12 (48.30, 55.92)	194	29.39 (26.04, 32.99)	122	18.00 (15.70, 21.64)	
Outer regional	169	53.82 (48.27, 59.28)	80	25.00 (20.95, 30.60)	65	20.70 (16.57, 25.55)	
Remote or very remote	30	66.67 (51.65, 78.92)	11	24.44 (13.99, 39.16)	4	8.89 (3.34, 21.61)	
Socioeconomic status							
Q_1 (lowest 20%) (ref)	258	50.00 (45.69, 54.31)	133	25.78 (22.18, 29.73)	125	24.22 (20.72, 28.12)	< 0.001
Q_2	312	52.44 (48.41, 56.43)	163	27.39 (23.96, 31.13)	120	20.17 (17.13, 23.59)	
Q_3	280	60.48 (55.94, 64.84)	120	25.92 (22.12, 30.11)	63	13.61 (10.77, 17.05)	

Table 2 Association of severity of disability and characteristics of cancer patients *(Continued)*

Variables	Severity of disability						
	No disability		Moderate disability		Severe disability		*P*-value
Q_4	329	61.61 (57.41, 65.65)	119	22.28 (18.95, 26.02)	86	16.10 (13.22, 19.48)	
Q_5 *(highest 20%)*	309	66.74 (62.31, 70.89)	97	20.95 (17.48, 24.90)	57	12.31 (9.61, 15.63)	
Overall	1488	57.88 (55.96, 59.77)	632	24.58 (22.95, 26.29)	451	17.54 (16.12, 19.06)	

P-value was derived using chi-square test or one way analysis of variance (ANOVA) where appropriate

patients are unable to return to employment after their diagnosis [20].

Furthermore, work disability leads to a substantial economic burden on society, individuals and their families, resulting in a reduction of $1.7 billion annually to GDP in Australia [20] and an approximately 5% GDP reduction in the Organisation for Economic Co-operation and Development (OECD) countries [44]. Therefore, cancer survivors may require psycho-social healthcare services and other therapeutic modalities, such as physical and occupational therapy, to assist in their return to a productive work life. Cancer patients with physically demanding jobs may require assistance during treatment, and possibly physical rehabilitation following treatment, in order to minimize morbidity. However, developing new and improved treatments with fewer side effects is another potentially important strategy to reduce cancer-related disability.

The results indicate that elderly cancer patients (older than 65 years) were at a significantly higher risk of having an extreme disability compared with younger patients (< 25 years). This finding is consistent with a previous study, which revealed that elderly cancer patients reported significantly more functional disabilities [45], required more assistance with daily living activities [46], and had deficits in performing work-related activities in terms of their physical ability [41, 47]. Thus, several factors might influence the reduction in their physical functioning. For example, a course of advanced cancer treatment is associated with considerable physical and psychological side effects in elderly cancer patients (e.g., weight change, muscle loss, fatigue and physical weakness) [48], and having multiple comorbidities [3, 27, 29] will presumably contribute to reduced daily activities. Moreover, an elderly cancer patient may have a limited acceptance of advanced treatment and health outcomes that may then contribute to a greater burden of health [48]. This result indicates that rehabilitation-related interventions (e.g., occupational and physical therapies) are essential to prevent ongoing work disability of cancer patients [49], and is an emerging cancer research area, particularly focused on the elderly [50].

The study results found that low level or no physical activities in cancer patients was strongly associated with an extreme level of work-related disability compared

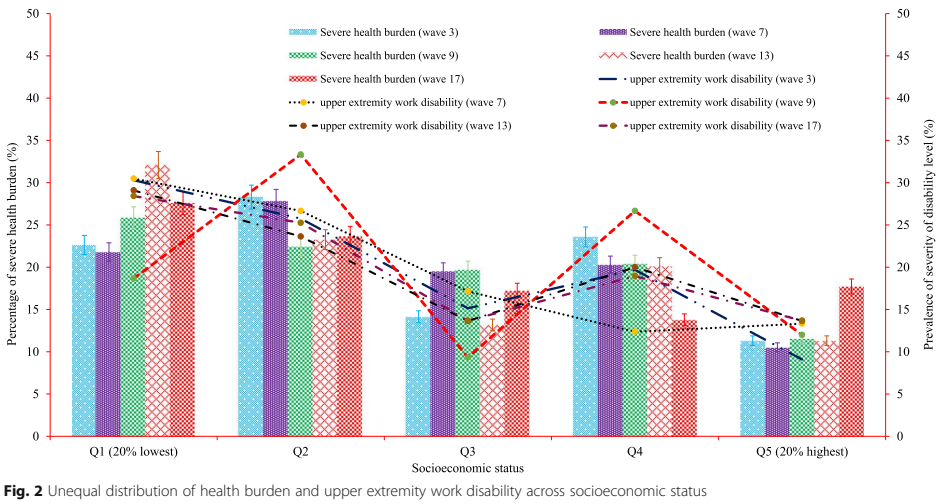

Fig. 2 Unequal distribution of health burden and upper extremity work disability across socioeconomic status

Table 3 Factors influencing severity of disability of cancer patients

Variables	Moderate disability vs No disability		Severe disability vs No disability	
	Un-adjusted model	Adjusted model	Un-adjusted model	Adjusted model
	RRR (95% CI)	RRR (95% CI)	RRR (95% CI)	RRR (95% CI)
Health burden				
No burden (= ref)	1.00	1.00	1.00	1.00
Moderate burden	7.88*** (4.26, 10.04)	4.03*** (3.56, 9.99)	5.66*** (4.35, 7.79)	5.92** (1.38, 25.40)
Severe burden	7.27*** (6.28, 18.4)	5.43*** (3.34, 7.81)	6.80*** (4.78, 9.09)	5.32*** (2.75, 11.60)
Female (ref = male)	1.08 (0.89, 1.30)		1.00 (0.81, 1.24)	
Age				
< 25 years (= ref)	1.00	1.00	1.00	1.00
25–45 years	1.09 (0.51, 2.35)	1.12 (0.37, 3.37)	0.75 (0.33, 1.70)	0.85 (0.24, 2.97)
46–65 years	1.80 (0.87, 3.75)	1.31 (0.47, 3.66)	1.47 (0.68, 3.18)	1.39 (0.45, 4.34)
> 65 years	3.23*** (1.56, 6.68)	1.40** (1.09, 4.00)	2.62*** (1.22, 5.63)	1.82*** (1.57, 5.87)
Educational achievement				
Year 11 or below (= ref)	1.00	1.00	1.00	1.00
Year 12	0.42*** (0.28, 0.62)	1.36 (0.82, 2.24)	0.57*** (0.38, 0.85)	0.77 (0.43, 1.39)
Trade/certificate/diploma	0.69*** (0.56, 0.85)	1.10 (0.51, 2.36)	0.60*** (0.47, 0.76)	1.54 (0.68, 3.47)
Tertiary or university	0.51*** (0.38, 0.68)	1.00 (0.62, 1.61)	0.37*** (0.26, 0.53)	0.77 (0.43, 1.36)
Unemployed (ref = employed)	2.97*** (3.65, 0.62)	1.55** (1.01, 2.39)	4.88*** (6.37, 0.85)	2.01*** (1.15, 3.50)
Marital status				
Single (= ref)	1.00	1.00	1.00	1.00
Married	1.68*** (1.22, 2.32)	1.41 (0.79, 2.54)	1.33 (0.94, 1.88)	0.69 (0.37, 1.31)
Others	2.25*** (1.60, 3.16)	1.44 (0.79, 2.62)	1.86*** (1.29, 2.68)	0.89 (0.47, 1.69)
Physical activity status				
Low	1.73*** (1.19, 2.51)	0.98 (0.64, 1.50)	5.17*** (3.11, 8.60)	1.91** (1.07, 3.40)
Moderate	1.64*** (1.11, 2.41)	1.30 (0.85, 2.00)	2.14*** (1.22, 3.75)	1.43 (0.77, 2.65)
High (= ref)	1.00	1.00	1.00	1.00
Alcohol consumption (ref = no)	1.54*** (1.25, 1.91)	0.94 (0.65, 1.35)	2.29*** (1.83, 2.88)	1.29*** (1.15, 1.49)
Smoking exposure (ref = no)	1.19 (0.91, 1.56)		1.07 (0.79, 1.45)	
Private insurance coverage (ref = yes)	1.22 (0.91, 1.62)	0.88 (0.62, 1.24)	1.68*** (1.22, 2.32)	1.02 (0.68, 1.53)
Healthcare utilisation (ref = yes)	4.62*** (3.34, 6.39)	0.29*** (0.19, 0.44)	8.13*** (5.15, 12.83)	0.34*** (0.20, 0.60)
Life satisfaction with				
Household members	1.02 (0.97, 1.07)	1.00 (0.90, 1.10)	1.01 (0.95, 1.07)	1.01 (0.90, 1.13)
Employment	0.89*** (0.87, 0.91)	0.99 (0.95, 1.04)	0.81*** (0.79, 0.84)	0.96 (0.91, 1.02)
Financial situation	0.94*** (0.90, 0.98)	0.95 (0.88, 1.03)	0.88*** (0.84, 0.91)	0.94 (0.86, 1.02)
Social supports	0.97 (0.92, 1.02)	1.00 (0.90, 1.10)	0.89*** (0.84, 0.94)	0.98 (0.88, 1.10)
Remoteness				
Major cities (= ref)	1.00	1.00	1.00	1.00
Inner regional	1.54*** (1.24, 1.90)	1.75*** (1.21, 2.52)	1.29* (1.01, 1.65)	1.60** (1.04, 2.48)
Outer regional	1.29 (0.96, 1.73)	0.95 (0.55, 1.63)	1.40* (1.02, 1.92)	1.27 (0.70, 2.31)
Remote or very remote	1.00 (0.50, 2.01)	0.80 (0.26, 2.43)	0.48 (0.17, 1.39)	0.22 (0.03, 1.81)
Socioeconomic status				
Q_1 *(lowest 20%)*	1.64*** (1.21, 2.24)	1.36** (1.09, 2.33)	2.63*** (1.84, 3.74)	1.28*** (1.16, 2.23)
Q_2	1.66*** (1.24, 2.24)	1.44 (0.87, 2.39)	2.09*** (1.47, 2.97)	1.25 (0.68, 2.32)
Q_3	1.37* (1.00, 1.87)	1.49 (0.87, 2.54)	1.22 (0.82, 1.81)	1.09 (0.56, 2.14)

Table 3 Factors influencing severity of disability of cancer patients *(Continued)*

Variables	Moderate disability vs No disability		Severe disability vs No disability	
	Un-adjusted model	Adjusted model	Un-adjusted model	Adjusted model
	RRR (95% CI)	RRR (95% CI)	RRR (95% CI)	RRR (95% CI)
Q_4	1.15 (0.85, 1.57)	1.21 (0.72, 2.01)	1.42 (0.98, 2.05)	1.36 (0.73, 2.52)
Q_5 *(highest 20%) (= ref)*	1.00	1.00	1.00	1.00

RRR Relative risk ratio, *CI* Confidence interval, *ref*. Reference group

with patients engaged in high-level physical activity. This finding is consistent with other research [38, 51–54], whereby authors found that limited physical activity levels were significantly associated with a higher risk of work disability among cancer patients. Further, a number of previous studies have proven that physical activity plays an effective role in ensuring improved health status [55], reducing the risk of developing future cancers [54], and also expressively contributing to lower mortality risk [56], which ultimately produces significant health benefits and reduces medical expenditures and treatment outcome disparities [55]. In terms of cancer risk, high levels of physical activities (compared with low levels) played a significant role in prevention of several cancers (e.g., 42% for gastrointestinal cancer, 23% for renal cancer, and 20% for myeloid leukemia) [57]. This included averting genetic damage, improving the immune system, reducing chronic infections, and controlling cancer cells [57]. Several hypotheses and mechanisms have been suggested regarding the anti-cancer effects of physical activities. The American Cancer Society guidelines for cancer survivors [58] recommend daily physical activities, including a continuation of normal daily life activities immediately after diagnosis, which help to significantly reduce physical stamina and muscle strength erosion as well as anxiety levels, thereby resulting in the prevention of long-term adverse health outcomes (e.g., work-related disability) [59].

This study results found an increased risk of work disability among cancer patients who consumed alcohol compared with patients who did not. In this study, alcohol consumption had a robust effect on patient outcomes. Formal drinkers represented two-thirds (≈ 75%) of the cohort and had a 46% greater risk of disability. The last Global Burden of Disease study, conducted in 2016, found a similar result, namely that alcohol consumption was a dominating determinant for higher risk of having a disability [60]. The World Health Organisation (WHO) has suggested that harmful alcohol consumption causes a high burden of disease, including cancer [61], which is often underappreciated [60]. This finding has further implications for the reform of public health policy, and decreasing population-level alcohol consumption should be recommended.

The risks of having an extreme disability level amongst cancer patients who lived in the poorest households were more pronounced compared with their richer counterparts. Recent studies have confirmed this result with disadvantaged socio-economic status of cancer survivors being negatively associated with long-term health effects or work-related disability [62, 63]. Some studies have also provided evidence that the magnitude of the cancer burden is negatively associated with socio-economic status [16, 31–34]. Furthermore, adverse health outcomes (e.g., worse health status, long and short-term disability and shorter life expectancy) were disproportionately found in poorer people as opposed to those with higher socio-economic status [13, 16, 31, 33, 64–71]. Contribtuing factors to the high rates of long term health impacts among the poorest groups includes higher tobacco rates [16, 27], economic burden [35, 36], increased mental illness [72], lack of health education and awareness [73], and less access to competent and effective health care services [73].

Low productivity, loss/reduction of household income, and increased healthcare expenditure are pronounced amongst the poorest cancer patients. Growing socio-economic inequalities of cancer outcomes need the attention of governments, health systems and decision makers. For example, Cancer Australia has an optimal care pathway project, which has already addressed several cancer types. Such initiatives might help to reduce socio-economic inequalities, which are related to poverty, gender, education, and health, and should promote universal access to health care which can further enhance both socio-economic and human development.

The ability to continue in the labour force, and allowing an individual the choice to do so, signifies a key aspect of the health status often threatened by disease. Long-term disability threatens the economic well-being of survivors and their families. Additionally, the health status of cancer patients who are restricted in their capacity to work may be affected by the loss of identity, life satisfaction, and social relationships that work often provides. Cancer survivorship, work disability and employment may be considered from different perspectives: the cancer survivor (e.g., health status, work disability level and return to employment), the caregiver and the family

(e.g., the health burden, reduction of socioeconomic position and risk for poverty), the employer and co-workers (e.g., employment conditions and workload), the health care provider (e.g., supportive care needs, effective programs and interventions), and the community or society (e.g., economic and policy changes).

This study includes some caveats. Study participants were accessed from the HILDA survey, which covers health, economic, employment, income and health characteristics of household members aged 15 years and older. Children who suffered from cancer were excluded from this study. Examining the long-term work disability is widely perceived to have substantial potential as an endpoint in health outcomes research; however, results are partially dependent upon study methods and outcome variables of interest. The participants of the present study were derived from the protocol "HILDA study" [32], wherein long-terms health conditions of cancer patients might change for independent study designs as well as application of survey instruments.

This study findings established a relationship between overall cancer burden and work-related disability among cancer survivors, which might vary in terms of cancer stages and types of cancer. The authors were not able to estimate the cancer-specific health burden nor the work disability of cancer survivors due to the paucity of relevant data. Further, the study findings were based on self-reported responses that might have been impacted by respondents' prejudice (e.g., silence and over-response), and by problems in understanding and interpreting the survey questions.

Despite these limitations, this study has noteworthy strengths including the use of a prospective design of long term follow-ups, and the application of well-validated and reliable longitudinal wave measures of the impacts of cancer diagnosis on the health burden and work disability of individuals over the 2003–2017 period. The study population was ethnically, geographically, and socio-economically diverse. Furthermore, this study included several potential confounding analytical factors that were not present in previous studies. For this study, data were gathered from five-waves of the HILDA survey of cancer survivors. The length of the survey period may have introduced uncontrolled bias, as changes in health status are not instantaneous and might emerge only after time, which was not captured in this study. Due to funding restrictions, the authors were unable to consider cancer patients who registered for cancer surveillance as well as received health care from health facilities (e.g., private clinics, community clinics, secondary or tertiary hospitals). Due to the paucity of cancer-related data in HILDA study, the authors were unable to perform cancer-specific analysis and period of treatment analysis. Future research is required using a similar study design, perspective and analytical methods in terms of cancer-specific exploration.

Conclusions

This study has identified a high rate of work-related disability that leads to a substantial decrease in a cancer survivor's socio-economic position. Several demographic, social, lifestyle and health burden variables were associated with the magnitude of disability. The findings have further implications for improving public health policy, and reducing population-level unhealthy lifestyle behaviours which should be recommended. The study results could be used to better outline the management of a sequelae course of treatment for those who should undergo more intensive physical rehabilitation aimed at reducing work disability levels. This may apply to cancer survivors who choose or need to work after cancer diagnosis and treatment especially those still active in the work force. This is important in light of the increasing prevalence of cancer and fortunately, the growing numbers of patients surviving cancer in Australia, and the likelihood of the development of impairments and activity limitations after cancer treatment. It is also significant for health care providers, including physical and occupational therapists and oncologists, who should be aware of the unique problems that challenge this population and who should advocate for prevention and evidence-based interventions. Therefore, it is recommended that effective and efficient cancer survivor-specific evidence-based interventions be developed to reduce the impacts of work disability by incorporating comprehensive social supports which ultimately, have the potential to affect the trajectory of the cancer burden in a positive way.

Abbreviations

IRSD: The index of relative socio-economic disadvantage; SES: Socioeconomic status,; SF-36: Short form; CI: Confidence Interval; HILDA: Household, Income and Labour Dynamics in Australia

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Consent to participate

Not Applicable.

Authors' contributions

Conceptualized the study: RAM; Contributed data extraction and analyses: RAM. Result interpretation: RAM. Prepared the first draft: RAM. Contributed during the conceptualization and interpretation of results and substantial revision: RAM, KA, JD and JG. Revised and finalized the final draft manuscript: RAM, KA, JD and JG. All authors read and approved the final version of the manuscript.

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Availability of data and materials
The Household, Income and Labour Dynamics in Australia (HILDA) data are used under strict licensing. Data can be potentially obtained subject to a peer-reviewed application. Further details are available at: https://www.melbourneinstitute.com/hilda/

Ethics approval and consent to participate
The present study was conducted based on secondary data source using a longitudinal data set from the Household, Income and Labour Dynamics in Australia (HILDA) survey over an extended period of 2003 to 2017. Ethical approval was not required from an institutional review board because the patient information was de-identified. Appropriate approval was obtained for this study from the Department of Social Services to access the publicly available, de-identified longitudinal dataset. The findings and views reported in this paper, however, are those of the author and should not be attributed to either the DSS or the Melbourne Institute.

Consent for publication
Not Applicable.

Competing interests
The authors declare that they have no conflict of interest. Rashidul Alam Mahumud is an Associate Editor of this journal.

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Publisher's Note

2.5 Study 5

Prevention strategy of cancer: Economics of cancer vaccination in Australia

The Study 4 of this thesis captured the long-term impact of productivity-related work disability among cancer patients and consequences over an extended period. *Study 5* was to assess the prevention strategy of cancer vaccination regarding the economics context using economics evaluation (cost-effectiveness analysis). Study 5 included two articles such as *Article V* examined evidence of the cost-effectiveness evaluation of the 9-valent *HPV* vaccine within a global context. Further, *Article VI* assessed the cost-effectiveness of adding a nonavalent new Gardasil-9® (*9vHPV*) vaccine to the national immunisation schedule in Australia across three different delivery strategies from the health system and societal perspectives.

Article V: Cost-effectiveness evaluations of the 9-valent human papillomavirus (*HPV*) vaccine: Evidence from a systematic review.

This review examined evidence of the cost-effectiveness evaluation of the 9-valent HPV vaccine within a global context. Searches were performed until 31 July 2019 using two databases: PubMed and Scopus. A combined checklist (i.e., WHO, Drummond and Consolidated Health Economic Evaluation Reporting Standards, *CHEERS*) was used to examine the quality of eligible studies. A total of 12 studies were eligible for review and nearly all were conducted in developed countries. Despite some heterogeneity in approaches to measuring cost-effectiveness, ten studies concluded that 9vHPV vaccination was cost-effective while two studies were not. The addition of adolescent boys into immunisation program was cost effective when vaccine price and coverage was comparatively low. When vaccination coverage for female was more than 75%, gender neutral *HPV* vaccination was less cost-effective than when targeting only girls aged 9–18 years. Multi cohort immunization approach was cost-effective in the age range of 9–14 years but the upper age limit at which vaccination was no longer cost-effective requires to be further evaluated. Most dominating parameters determined were

duration of vaccine protection, time horizon, vaccine price, coverage, healthcare costs, efficacy and discounting rates. These findings are anticipated to support policymakers in extending *HPV* immunization programs on either switching to the 9-valent vaccine or inclusion of adolescent boys' vaccination or extending the age of vaccination. Further, this review also supports extending vaccination to low-resource settings where vaccine prices are competitive, donor funding is offered, cervical cancer burden is high and screening options are limited.

Article VI: The cost-effectiveness of controlling cervical cancer using a new 9-valent human papillomavirus vaccine among school-aged girls in Australia

The objective of *Study 5* was to assess the cost-effectiveness of adding a nonavalent new Gardasil-9® (*9vHPV*) vaccine to the national immunisation schedule in Australia across three different delivery strategies from the health system and societal perspectives. This study was an extensive cost-effectiveness analysis of *9vHPV* vaccination in Australia from both the health system and societal perspectives. The introduction of the *9vHPV* immunisation was assessed to be very cost-effective from both perspectives. It incorporated three delivery strategies (school-based, health facility-based, and outreach-based). However, this high-value vaccination would need substantial upfront investments. Considering a two-dose schedule, the *9vHPV* vaccination demonstrated 'good value for money', if the vaccination could accomplish a high vaccination coverage and provide protection. The findings of this evaluation contribute to decision-making about the incorporation of the *9vHPV* vaccine into a universal cervical cancer vaccination program in Australia. With continued assessment of the potential vaccine properties as well as vaccine delivery and scale-up strategies, the two-dose *9vHPV* vaccine would provide significant health and economic benefits for preadolescents and society. Finally, the success of *9vHPV* vaccination will be contingent on several predominating factors, including value for money, feasibility, acceptability, and affordability.

RESEARCH ARTICLE

Cost-effectiveness evaluations of the 9-Valent human papillomavirus (HPV) vaccine: Evidence from a systematic review

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Abstract

Introduction

The World Health Organization (*WHO*) recommends that human papillomavirus (*HPV*) vaccination programs are established to be cost-effective before implementation. WHO recommends HPV vaccination for girls aged 9–13 years to tackle the high burden of cervical cancer. This review examined the existing evidence on the cost-effectiveness of the 9-valent HPV vaccine within a global context.

Methods

The literature search covering a period of January 2000 to 31 July 2019 was conducted in *PubMed* and *Scopus* bibliographic databases. A combined checklist (i.e., *WHO*, Drummond and *CHEERS*) was used to examine the quality of eligible studies. A total of 12 studies were eligible for this review and most of them were conducted in developed countries.

Results

Despite some heterogeneity in approaches to measure cost-effectiveness, ten studies concluded that *9vHPV* vaccination was cost-effective and two did not. The addition of adolescent boys into immunisation programs was cost effective when vaccine price and coverage was comparatively low. When vaccination coverage for females was more than 75%, gender neutral *HPV* vaccination was less cost-effective than vaccination targeting only girls aged 9–18 years. Multi cohort immunization approach was found cost-effective in the age range of 9–14 years. However, the upper age limit at which vaccination was found not cost-

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effective requires further evaluation. This review identified duration of vaccine protection, time horizon, vaccine price, coverage, healthcare costs, efficacy and discounting rates as the most dominating parameters in determining cost-effectiveness.

Conclusions

These findings have implications in extending *HPV* immunization programs whether switching to the 9-valent vaccine or the inclusion of adolescent boys' vaccination or extending the age of vaccination. Further, this review also supports extending vaccination programs to low-resource settings where vaccine prices are competitive, donor funding is available, burden of cervical cancer is high and screening options are limited.

Introduction

Cervical cancer (*CC*) is the third most common cancer and the leading cause of cancer-related deaths in women worldwide [1]. Approximately 570,000 new cases of *CC* were diagnosed in 2018, composing 6.6% of all cancers in women [1]. The burden of *CC* is an alarming issue across the globe, especially in low-and middle-income countries (*LMICs*). Approximately 85% of *CC* cases and 90% of deaths from *CC* occur in *LMICs* [1]. Persistent infections with human papillomavirus (*HPV*) are a key cause of *CC* and is an established carcinogen of *CC* [2]. *HPV* is predominantly transmitted to women of reproductive age through sexual contact [3]. Most *HPV* infections are transient and can be cleared up within a short period, usually a few months after their acquisition. However, untreated *HPV* infections can continue and evolve into cancer in some cases. There are more than 100 types of *HPV* infections, and high-risk types develop into *CC* [4]. Thirteen high-risk *HPV* genotypes are known to be predominantly responsible for malignant and premalignant lesions of the anogenital area [5], and these are the leading causes of most aggressive *CC* [6]. Further, *HPV* is also responsible for the majority of anogenital cervical cancers, including anal cancers (88%), vulvar cancers (43%), invasive vaginal carcinomas (70%), and all penile cancers (50%) globally [4].

The burden of *CC* (i.e., high incidence and mortality rates) globally is preventable through the implementation of a primary prevention strategy such as vaccination [1]. There are vaccines that can protect common cancer-causing types of *HPV* and reduce the risk of CC significantly. Three types of *HPV* vaccines, namely *bivalent* (Cervarix), *quadrivalent* (Gardasil) and 9-valent vaccine (Gardasil-9), are currently available in the market. Unfortunately, as of March 2017, only 71 countries (37% of all countries) have included *HPV* vaccines in their national immunization programs for girls, and 11 countries (6%) included for both sexes [2]. The first global recommendation on *HPV* vaccination was proposed by the World Health Organization's Strategic Advisory Group of Experts on Immunization in October 2008 [7], where *HPV* vaccination was recommended for girls aged 9–13 years. This recommendation was updated in April 2014 [8], with the emphasis to include extended 2-dose *HPV* immunization for girls aged 9–14 years, who were not immune compromised. With the recent licensing of the 9-valent vaccine and the introduction of various *HPV* vaccination strategies, an update on the current recommendations of *HPV* vaccination are inevitable. The goals of the immunisation program are to combat the acquisition and spread of *HPV* infections, and achieving optimum coverage through effective delivery systems. According to the underlying distribution of *HPV* infection types of *CC*, the *9vHPV* vaccine builds population-level strong immunity against *HPV*-6, 11, 16, 18, 31, 33, 45, 52, and 58 infections [5] that cumulatively contributed

approximately 89% of all *CCs* globally [9]. With respect to the primary prevention of *HPV* infection, it is expected that the *9vHPV* vaccine can reduce the lifetime risk of diagnosis with *CC* by an additional 10% in immunised cohorts compared with the *4vHPV* vaccine and by an additional 52% in non-vaccinated cohorts [10].

This review aims to update the current evidence on the economic viability of *HPV* vaccination. In addition, this study aims to examine the cost-effectiveness of the 9-valent vaccine when boys are included and when age cohorts are varied, from the global context. This review may be used as comprehensive evidence of general trends on the ongoing cost-effectiveness evaluation of *HPV* vaccine.

Materials and methods

Study design

Published original academic literature that examined the cost-effectiveness of *9vHPV* vaccination were included in this systematic review. A wide type of study perspectives including societal and health systems perspectives were employed. A search strategy was adopted considering all countries regardless of perspective or vaccine delivery strategy. A combined *WHO* [11], Drummond [12] and *CHEERS* [13] checklist was used to evaluate the quality of included studies.

Search strategy and sources

A literature search for the period of January 2000 to 31 July 2019 was conducted using *PubMed* and *Scopus* bibliographic databases. This study searched for articles with no language restrictions. The literature search was performed by searching Scopus and PubMed databases to identify relevant articles following the inclusion criteria. Search inclusion terms included 'economic evaluation', 'cost-effectiveness', 'analysis', 'human papillomavirus', '*HPV*', 'vaccine', 'vaccinated', 'vaccination', 'cervical cancer', 'non-valent', '9 or nine-valent' (Appendix A). Reference lists for selected studies were checked to identify relevant studies for inclusion.

Study selection

Three authors (*RAM*, *SAK and GMO*) of the review team independently examined the titles and abstracts of the articles that met the selection criteria. The existing academic literature in the cost-effectiveness of *9vHPV* vaccination was searched. Language restrictions were not applied. The eligibility of studies for inclusion was determined following a three-stage screening process. The first stage involved screening studies by title to eliminate duplicates. The second stage required the reading of abstracts to determine their relevance to this study. The third stage necessitated the reading of full texts of the retained studies as reflected in Fig 1. *RAM* carried out and recorded the above process, and shared the record with *SAK and GMO* for verification. Discrepancies were discussed and resolved by consensus.

Data checking

The study strategy followed a number of checks to ensure consistency of approach, including a discussion about discrepancies within the study team. For each outcome and model input parameters, the authors identified the proportion of missing observations. Datasets were combined to form a new master dataset where model input assumptions and outcome-related parameters used in the original studies were included. Further, three authors independently assessed the analytical quality of the preliminary selected studies using appropriate tools for

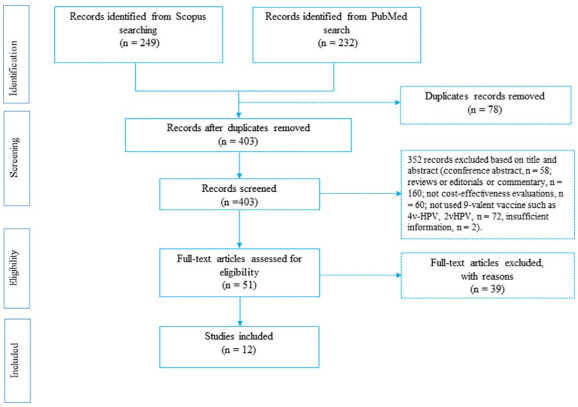

Fig 1. PRISMA flow-chart for systematic review of studies.

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examining risk of bias. Disagreements on inclusions were resolved by discussion with a third review author.

Data extraction (selection and coding)

The study selection process was conducted following the *PRISMA* guidelines [14]. Data were extracted to develop a comprehensive data matrix which summarises the study characteristics such as authors, settings, perspective, threshold, outcome-related parameters and other necessary information.

Strategy for data synthesis

Three authors (*RAM*, *SAK and GMO*) independently reviewed the titles and abstract. Data from all eligible studies were extracted by the same two authors using a standardized data collection form. A matrix was developed to summarise the characteristics and findings of the studies. Studies were characterized by incorporating four themes: (i) study used *9vHPV* vaccine to examine the cost-effectiveness, (ii) target population demographic characteristics (e.g., gender-neutral and multiple age cohort immunisation), (iii) study perspectives, model and economic level of each country, and (iv) model input and outcome-related parameters.

To compare findings across the selected studies, incremental cost-effectiveness ratios (*ICERs*) and standardized cost-effectiveness were outlined. In terms of standardized cost-effectiveness scenarios, these studies used the heuristic cost-effectiveness threshold guided by the *WHO* [15], wherein an intervention or program was evaluated to be cost-effective if the *ICER/DALYs* averted was less than three times a country's annual per capita Gross Domestic Product (*GDP*). Further, the *WHO* constructed three broad decision rules: (i) an intervention or program was recommended as very cost-effective if *ICER/DALYs* averted <1 time *GDP* threshold; (ii) cost-effective if *ICER/DALYs* averted ≥ 1 time *GDP* threshold and ≤ 3 times *GDP* threshold; and (iii) not cost-effective if *ICER/DALYs* averted >3 times *GDP* threshold [16]. Examining whether an *ICER* offered by any strategy signifies value for money requires comparison to a cost-effectiveness threshold (*CET*). The *CET* refers to the health effects foregone (i.e., opportunity costs) related to resources being devoted to an intervention and consequentially being

unavailable for other health-care priorities. Policy makers should be willing to invest their limited resources in the strategy offering the greatest health gains. The review may serve as an important evidence with respect to methodological and current practices of cost-effectiveness evaluation studies such as determination of study research questions; the study perspective adopted, the duration of vaccine protection, time horizon and discount rate; explanation of model performed for data analysis; model input assumptions behind the estimation of associated costs and outcome parameters; reporting of *ICERs*; most dominant parameters of sensitivity analysis; examination of study conclusions and recommendations as well as financial disclosure of the selected studies.

Study characteristics

Four hundred and eighty-one articles were yielded through the primary search, of which 78 articles were discarded because of duplication. Fifty-one articles were considered for full-text review after screening by title and abstract. Of these, 12 articles were eligible for the final review (Table 1). Three hundred fifty-two articles were excluded from this study following the inclusion criteria. The reasons for exclusion were: conference abstract (n = 58), reviews or editorials or commentary (n = 160), not cost-effectiveness evaluations (n = 60), did not use 9-valent vaccine (*4v-HPV*, *2v-HPV*; n = 72) and insufficient information (n = 2). Finally, 12 articles were included in this review (Fig 1).

Settings and funding

Single country studies mostly focused on high-income settings [4,17,26–28,18–25] (Table 2). However, a single study was found that covered two low-income countries (e.g., Kenya and Uganda) [29]. Eight studies were funded by research organisations [4,17,19,21–24,29], while two studies did not state funding sources [20,27]. The Bill and Melinda Gates Foundation was the sole funder of one study [29] and three studies were funded by the Centre for Disease Control (*CDC*) [21,24,27]. Further, five studies were conducted in United States [20,22,24,27,28], one study was conducted in each of Germany [23], Italy [4], China [18], Australia [25], Austria [17], and Canada [19]. Low resource countries mostly depend on external funding agency for *HPV* vaccine programs, hence these countries may have less impetus for cost-effectiveness studies to inform local decision making as priorities are driven by external considerations.

Study questions

Most studies (8 out of 12 studies) investigated the cost-effectiveness of introducing *9vHPV* vaccination to preadolescent girls aged 12 or younger [4,17–19,22,24–26,29]. Four studies assessed vaccinating 12 years or older girls [20,23,27,28]. All studies investigated vaccination either as an addition to existing screening programs or (more commonly) as opportunistic preventive programs or none at all. Further, most studies considered a range of vaccination and screening options to find the most cost-effective combination.

Analytical model

Nine studies used a dynamic economic model for examining the cost-effectiveness of *HPV* vaccination programs [4,17,27,28,18,20–26], two studies used a static model [19,29], and one study used a Markov model for analytical exploration [18] (Table 2). However, some studies did not explicitly account for the pathologic transition from *HPV*-acquisition to *HPV*-associated disease [4,18,25,27,28], pathologic transition [4,23] and herd immunity [17,19,20,24,27,28].

Table 1. Characteristics of twelve included cost-effectiveness studies of *9vHPV* vaccination.

Characteristics	Number of studies (n)	Percentage (%)
Selected articles	12	100
Year of publication		
2014	2	17
2016	7	58
2017	2	17
2018	1	8
Name of Journal		
BMC Infectious Diseases	2	17
Cost Effectiveness and Resource Allocation	1	8
Expert Review of Pharmacoeconomics & Outcomes Research	1	8
Human Vaccines & Immunotherapeutics	1	8
International Journal of Cancer	1	8
The Lancet Public Health	1	8
PLoS ONE	1	8
The Journal of Infectious Diseases	2	17
Vaccine	1	8
Journal of the National Cancer Institute	1	8
Study setting		
Australia	1	8
Austria	1	8
Canada	1	8
China	1	8
Germany	1	8
Italy	1	8
Kenya and Uganda	1	8
United States	5	42
Main location of first author		
Research institute	8	67
Research group	1	8
Hospital or University	3	25
Conflict of interest		
Yes	6	50
No	6	50

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Thresholds and perspectives

In terms of the cost-effectiveness scenario, four studies used the heuristic cost-effectiveness threshold proposed by the *WHO*. These studies used either one or three times *GDP* per capita [18,19,24,29]. The majority of studies adopted local thresholds (e.g., willingness to pay) while three studies considered both thresholds of *GDP* per capita and willingness to pay [18,24,29]. Apart from these studies, seven studies undertook an evaluation from a societal perspective [19,22–24,27–29], and four studies utilised the health system perspective [4,18,20,25]. Several studies used the societal perspective and included all vaccination costs, relevant direct medical costs, and gains in quality and length of life without considering who incurred the costs or who received the benefits (Table 2). However, these selected studies reported little about the indirect costs and productivity losses which are significant from the societal perspective.

Table 2. Characteristics of the selected studies.

Author	Study settings	Economic category	Target age cohort	Sex of cohort	Vaccine delivery route	No of doses	Type of model	Threshold	Perspective	Time horizon (year)	Discount rate	Sensitivity analysis	Most sensitive parameter
Kiatpongsan et al. [29]	Kenya and Uganda	LMIC	9 years	Female	NIP	3	Static	GDP and WTP	Societal	ns	3%	One-way	Discount rate
Laprise et al. [22]	United States	HI	9–14 years	Female	NIP	2 & 3	Dynamic	WTP	Societal	100	3%	One-way	Vaccine efficacy, screening method, and healthcare costs, vaccine coverage
Largeron et al. [23]	Germany	HI	12–17 years	Female	SHI plans	2	Dynamic	WTP	Societal	100	3%	One-way	Discounted rate, vaccine price
Mennini et al. [4]	Italy	HI	12 years	Female	NIP	2	Dynamic	WTP	Health system	100	3%	One-way	Vaccine price
Mo et al. [18]	China	MI	12 years	Female	NIP	3	Markov	GDP and WTP	Health system		3%	One-way	
Simms et al. [25]	Australia	HI	12 years	Female	NIP	2	Dynamic	WTP	Health system	20	5%	One-way	Vaccine price and vaccine duration of protection
Boiron et al. [17]	Austria	HI	9 years	Gender-neutral	Universal	2	Dynamic	WTP & GDP	Health system	100	3%	One-way	Discount rates and duration of protection
Brisson et al. [24]	United States	HI	9 years	Gender-neutral	Universal	3	Dynamic	WTP	Societal	70	3%	One-way	Vaccine price
Chesson et al. [27]	United States	HI	Female: 12 to 26 years, and male:12 to 21 years	Gender-neutral	NIP	3	Dynamic	WTP	Societal	100	3%	One-way	Vaccine price, Time horizon
Chesson et al. [28]	United States	HI	Female:13-18years	female	NIP	3	Dynamic	WTP	Societal	100	3%	One-way, Multi-way	Vaccine price
Chesson et al. [20]	United States	HI	Female: 12 to 26 years, and male:12 to 21 years	Gender-neutral	NIP	3	Dynamic	WTP	Health system	100	3%	One-way, Multi-way	Vaccine price
Drolet et al. [19]	Canada	HI	10 years	Female	NIP	3	Static	GDP	Societal	70	3%	One-way, Multi-way	Duration of protection, vaccine efficacy, vaccine price, discount rate

SHI = Statutory health insurance plans, NIP = National Immunisation Program, WTP = Willingness to pay

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Vaccine coverage

The assumptions on vaccine coverage are significant in influencing the potential impact of *HPV* vaccine on *HPV* related diseases. Four selected studies assumed a vaccination coverage rate of 90% or above [18,22,23,29]. The vaccine coverage might be varied in terms of study settings as well as from a gender point of view. Among the selected studies, three studies considered vaccine coverage rates of 26–60% for females and 25–40% for males [17,27,28], and three studies considered a 46–80% vaccine coverage rate [19,20,25]. Three studies grouped vaccination coverage rate by gender, assumed 25–60% for females and 11–40% for males [24,27,28]. The remaining studies did not specify the vaccination coverage rate [24].

Vaccine efficacy

Most studies considered a vaccine efficacy rate ranged from 95–100% against *HPV* infections except the study of Simms et al. (2016) [25], which considered a vaccine efficacy rate of only 59%. The study conducted in two East African countries (Kenya and Uganda) used a 100% vaccine efficacy rate in case of *9vHPV* [29]. Most studies (n = 10/12) used a 95% vaccine efficacy rate [4,17,27,28,18–24,26].

Number of vaccine dose and delivery route

Eight studies used a three-dose schedule of *9vHPV* vaccine. Most studies were conducted in developed countries [18–21,24,27–29] and the other two studies were conducted in low- and middle-income countries (*LMICs*) [18,29]. Further, one study conducted in the United States [21] used both 2- and 3-dose vaccines. Diverse vaccine delivery routes were evidenced across the selected studies. Nine studies used the vaccine delivery route of a national immunisation program for the target population [4,18–21,25,27–29]. Two studies conducted in Austria [17] and United States [24], used a universal immunisation strategy to deliver the vaccine. Only one cost-effectiveness exploration of *9vHPV* vaccine was conducted in Germany [23] and it used a vaccine delivery route through social health insurance.

Duration of vaccine protection, herd immunity effect, and discounting rate

Most studies (11/12) assumed lifelong vaccine protection while only one study assumed a shorter duration of protection of 20 years [19]. Half of the studies specified herd immunity due to vaccination [17,19,20,24,27,28]. The remaining six studies did not consider the indirect effect of vaccination. Regarding the discount rate, majority of the studies (11/12) used 3% discount rate, while one study considered a 5% discount rate to adjust for future values in terms of economic value and health outcome [25].

Quality of included studies

The quality scores were assigned using the Consensus Health Economic Criteria (*CHEC*) list, a checklist that can be used to critically evaluate published economic evaluations [30]. Table 3 showed the extent to which the reviewed studies followed the standards of reporting economic evaluations based on the *WHO* guidance [11], Drummond [12] and the Consolidated Health Economic Evaluation Reporting Standards (*CHEERS)* [13]. All studies clearly identified the study question, intervention(s), comparator(s) perspectives, time horizon and discounting rates. Most studies performed sensitivity analyses (11/12; 92%) to assess the robustness of concerned study findings. Most studies clearly described the measurements and the assumptions for measuring the costs (11/12, 92%). The choice of model used was justified in all studies, where dynamic transmission model was adopted to capture herd immunity. The currency and price data were also

Table 3. Extent to which included studies met standard reporting recommendations.

Explained recommendations	Number of studies fulfilling	Percentage (%)
Research question or objective clearly stated	10/12	83
Described intervention and comparator	10/12	83
Exploration of effectiveness reported	11/12	92
Single study-based estimates	8/12	67
Synthesis-based estimates	10/12	83
Assumption of costs and outcomes specified	11/12	92
Currency and price data reported	12	100
Choice of model justified	12	100
Perspective specified	12	100
Time horizon specified	12	100
Discounting rates specified	12	100
Calculated and reported *ICER* or cost-saving	12	100
Sensitivity analysis performed	11/12	92
Conclusions follow from the data reported	12	100
Disclosed funding source(s)	10/12	83

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reported in all studies. 10 (83%) out 12 studies disclosed the funding sources. However, only 8 studies (67%) reported the measurement of effectiveness from synthesis-based estimates, either through the combination of several randomized trials or the use of systematic reviews.

Results

Ten studies concluded that their evaluation of *9vHPV* vaccination was found to be cost-effective (Table 4) while the remaining two studies did not find cost-effectiveness [27,28]. Further, five studies exhibited a 'very cost-effective' decision [4,18,19,23,29] and four studies found 'cost-savings' [17,22,24,27]. In the context of high-income countries (e.g., Canada and Austria), introduction of *9vHPV* vaccination was a cost-effective decision to prevent cervical cancer in adolescent girls, as the incremental cost of vaccine was less than US$23-US$47. However, in low and middle-income countries (e.g., Kenya and Uganda), the *ICER* of *9vHPV* vaccine must not be priced over US$8.40-US$9.80 [19,29]. Two *US based* studies concluded that the cost-effectiveness exploration of *9vHPV* vaccine was more likely to be 'cost-saving' regardless of cross-protection assumption [24,27]. Most studies used 'quality-adjusted life year' (*QALYs*) as the unit of measurement. In addition, selected studies explored the cost-effectiveness decision using *WTP* thresholds that depend on country settings. Cost-effectiveness decision differs with country specific vaccine prices. For example, two studies conducted in the *US*, considered two different vaccine prices per dose, US$162.74 and US$174, respectively. However, both studies confirmed that the introduction of *9vHPV* vaccine was not cost-effective. Four studies reported cost-effectiveness of *9vHPV* vaccine for gender-neutral approaches [17,20,24,27] and three studies found it a 'cost-effective' or 'cost-saving' decision [17,24,27]. The remaining eight studies suggested vaccinating girls only. In terms of key drivers of cost-effectiveness, this review identified duration of vaccine protection [17,19,25], time horizon [28], vaccine price [4,19,20,23–25,27,28], healthcare costs [22], vaccine efficacy [19,22], vaccine coverage [19,22] and discounting rates [17,19,23,29] as the most influential parameters.

Discussion

The *HPV* vaccination is one of the cornerstones of *CC* prevention worldwide. This study explored the cost-effectiveness of *9vHPV* vaccination by reviewing 12 cost-effectiveness

Table 4. Summary of the results of the selected studies.

Author	Vaccine efficacy	Vaccine coverage	Duration of vaccine protection	Herd effect	Vaccine price per dose	Unit of cost-effectiveness	GDP per capita	Incremental cost-effectiveness ration (ICER)	Conclusion or recommendation	Study funder
Kiatpongsan et al. [29]	100%	100%	Lifetime	No	US$ 90.25	QALYs	Kenya = $1,349.97, Uganda = $ 674.05	Very cost-effective if additional cost of 9vHPV vaccine per course ≤ $9.8 in Kenya & ≤ 8.4 in Uganda	Very cost-effective for both countries (Kenya & Uganda)	The Bill and Melinda Gates Foundation
Laprise et al. [22]	95%	90%	Lifetime	No	US$ 158	QALYs		Cost saving to US $ 500	Cost saving	CDC
Largeron et al. [23]	96%	90%	Lifetime	No	€ 140	QALYs	£30,000	€ 329 / QALY	Highly cost-effective	Sanofi Pasteur MSD (SPMSD).
Mennini et al. [4]	96%	90%	lifelong	No	€ 80.00	QALYs	€ 40,000	€ 10,463 / QALY	Highly cost-effective	Sanofi Pasteur MSD
Mo et al. [18]	96.7%	20%	lifetime	No	USD 149.03	QALYs	USD 23,880	US$ 5,768 / QALY	Highly cost-effective with screening 1 + 9vHPV,—Cost-effective with screening 2 + 9vHPV	The Japan Society for the Promotion of Sciences, the National Centre for Child Health and Development, and the Chinese Natural Sciences Foundation
Simms et al. [25]	59%	70%	lifelong	No	ns	QALYs	AUD 30,000	Cost-effectiveness if the additional cost per dose is US$18–28	Cost-effective	National Health and Medical Research Council, Australia
Boiron et al. [17]	98%	Female: 60% Male: 40%	Lifelong	Yes	US$ 147.15	QALYs	US$ 44,767.35	Cost-saving at vaccine price up to US$ 166.77	Cost-saving	Sanofi Pasteur MSD
Brisson et al. [24]	95.0%	Not stated	Lifelong	Yes	US$ 158	QALYs	US$ 48,373.88	Cost-saving regardless of cross-protection assumptions	Cost-saving if additional cost of vaccine per dose < US$ 13	CDC, Canadian Research Chair Program
Chesson et al. [27]	95.0%	Female: 25.8% Male: 11.7%	Lifelong	Yes	US$ 162.74	QALYs	US$ 52,787.03	Cost-saving regardless of cross-protection assumptions (<$0)	Cost-saving	Not stated
Chesson et al. [28]	95.0%	Female: 46% Male: 25%	Lifelong	Yes	US$ 162.74	QALYs	US$ 52,787.03	US$ 111,446 / QALY	Not cost-effective	CDC, Canada Research Chair Program, Canadian Institute for Health Research
Chesson et al. [20]	95.0%	46%	Lifelong	Yes	US$ 174	QALYs	US$ 52,787.03	US$ 228,800 / QALY	Not cost-effective	Not stated
Drolet et al. [19]	95.0%	80%	20years	Yes	US$ 90.25	QALYs	US$ 50,440.44	US$ 11,593 /QALY	Very cost-effective if additional cost of vaccine per dose ≤ US$ 22.80	Canadian Research Chair Program

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evaluations in order to inform and expand knowledge on the cost-effectiveness of *9vHPV* vaccines. Most studies were conducted from a developed country perspective and two studies were performed from a *LMIC* perspective. However, a higher incidence of cervical cancer in *LMICs* is a serious public health concern, which warrants more evidence for effective decision

making [31]. The economic viability of gender-neutral *9vHPV* vaccination was confirmed by three studies [17,24,27]. Cost-effectiveness exploration depends on the coverage of vaccination from the perspective of gender. For example, if the vaccine coverage for female recipients is 80% or above, the majority of the anogenital *CC* including vulvar cancers, invasive vaginal carcinomas cancers in females could be prevented. As a result, introduction of *9vHPV* vaccination for boys is relatively less important compared with girls as high economic costs are involved without additional benefits gained, both from the societal and health system perspectives. Therefore, achieving optimal coverage of vaccination in females should remain a priority. This is of primary significance for *LMICs* settings since it is more effective and economically viable to prevent *CC* in females. However, it is also important to note that past studies paid little attention to the broader benefits of vaccination among male cohorts to prevent penile, anal, and oropharyngeal cancers. Exclusion of these diseases related to males may undermine the effectiveness of reducing *CC*. Gender-neutral vaccination might have several benefits including herd protection for boys. Moreover, it may provide indirect protection to unvaccinated women and direct protection to homosexual men. Therefore, this vaccination strategy should be further considered in country-level immunization programs by underlining other parameters including disease burden, sexual behaviour in a country (e.g., homosexual intercourse), equity, budget impact, and affordability.

Despite different methodologies and various assumptions, most studies were consistent in their conclusion that multiple age cohort vaccination was economically viable. Nevertheless, there was an upper age limit at which *HPV* vaccination was no longer cost-effective, and should be interpreted cautiously as several studies evaluated the cost-effectiveness in a single age range only and did not compare to the next age range in a progressive manner. Subsequently, this could result in an overestimation of the cut-off age range for vaccination. The protection duration from vaccination has a large impact on the cost-effectiveness of multi-cohort vaccination, with most studies assuming life-long protection. Therefore, the use of *ICERs* based on the conventional evaluation of 10-year protection may be more representative of real-life effectiveness rather than the use of *ICER* based on lifetime protection. The cost-effectiveness of *HPV* vaccination is also dependent upon the levels of vaccine coverage, compliance, and vaccine price.

Most studies presumed a high rate of vaccination coverage, e.g., assumed that 70% of the target population will receive full doses of vaccination. However, not everyone completed full doses (i.e., two or three doses) within the recommended time frame. Therefore, cost-effectiveness evaluation may underestimate or overestimate the actual costs and benefits. The analytical model outcomes in terms of herd immunity is only hypothetical unless the coverage level increases among the study cohort. Further, it is also indeterminate how non-compliance may consequently influence vaccine efficacy, effectiveness and duration of protection. Model input assumptions regarding the *9vHPV* vaccine price also influence the observed cost-effectiveness outcomes. Prices for *9vHPV* vaccine are currently not specified, particularly, in lower-income countries. Hence, the cost-effectiveness of *9vHPV* vaccine is still indeterminate and there is no exclusive evidence of greater cost-effectiveness than the older licensed *HPV* vaccines.

Therefore, once the 9-valent vaccine price is fixed, including support by the *GAVI* vaccine-alliance, reassessment of cost-effectiveness of *9vHPV* vaccine is necessary. Another model input assumption that may influence the cost-effectiveness is the inclusion or exclusion of herd immunity effects based on the type of model acceptance. Two studies [19,29] constituted the static model as an analytical exploration which did not confirm herd immunity effects. Generally, the cost-effectiveness evaluations of *HPV* vaccine should use a dynamic model for exploration because economic evaluations for primary prevention strategy should be determined by societal benefits (e.g., indirect impacts on population not immunised) rather than

individual demands [32]. However, the application of a static model in these two studies may underestimate or overestimate the benefits of vaccination. If an *HPV* vaccination program is exhibited to be cost-effective considering a static model for analytical exploration, it is anticipated to be even very cost-effective when a dynamic model is considered [32].

There are several types of cost-effectiveness threshold. The majority of the studies used the cost-effectiveness demand side-threshold (e.g. willingness-to-pay). In health-related explorations, a willingness-to-pay threshold signifies an evaluation of what a consumer of health care might be prepared to pay for the health benefit–given other competing demands on that consumer's resources. There are also supply-side thresholds that resource allocation mechanism takes into account. For example, estimates of health status are predetermined since when an insurance company or other provider spends some of its available budget on a new intervention it is therefore required to decrease its funding of previous interventions. In considering the choice of the type of cost-effectiveness threshold to use, the concept of opportunity cost may be the one most relevant to providers who are primarily concerned with using available resources to maximise improvements in health status. In response to the implementation of a new intervention, decision-makers need estimates of both the health that might be gained elsewhere through the alternative use of the resources needed for the new intervention and the health that is likely to be lost if the new intervention is not used.

This review has some limitations. The cost-effectiveness evaluation based on *GDP* based thresholds of 1–3 times of *GDP* per capita might be misleading for country-level decision making due to a lack of country specific thresholds [33]. It is uncertain whether this threshold truly reflects the country's affordability or societal willingness to pay for additional health gains. Additionally, *GDP* is originally intended to measure the experience of people residing in urban areas and thus it may not actually reflect the experience of the entire population in a country, especially those living in rural areas. Apart from an economic standpoint, other factors should be considered for the national immunization program, such as budget availability, political issues, cultural influences and availability of healthcare workforce.

Conclusions

There are a limited number of studies that showed conclusive evidence of cost-effectiveness of the *9vHPV* vaccine. The inclusion of adolescent males in *HPV* vaccination programs is cost-effective subject to vaccine price or coverage of females being low and *HPV*-associated male diseases are taken into account. Multiple age cohort vaccination strategy is likely to be cost-effective in the age range of 9–14 years, but the upper age limit at which *HPV* vaccination is no longer cost-effective requires further investigation. Vaccine coverage, price, duration of protection and discount rates are important parameters for considering the uptake of *HPV* vaccination. Nonetheless, the present study findings may serve as useful evidence for health policy-makers and healthcare providers in taking decision about *HPV* national immunization programs using the new *9vHPV* vaccine or inclusion of adolescent boys' for vaccination or extending the age of immunization.

Supporting information

S1 Checklist.
(DOC)

S1 Appendix.
(DOCX)

S1 Data.
(DTA)

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RESEARCH ARTICLE

The cost-effectiveness of controlling cervical cancer using a new 9-valent human papillomavirus vaccine among school-aged girls in Australia

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Abstract

Introduction

Cervical cancer imposes a substantial health burden worldwide including in Australia and is caused by persistent infection with one of 13 sexually transmitted high-risk human papillomavirus (*HPV*) types. The objective of this study was to assess the cost-effectiveness of adding a nonavalent new Gardasil-9® (*9vHPV*) vaccine to the national immunisation schedule in Australia across three different delivery strategies.

Materials and methods

The Papillomavirus Rapid Interface for Modelling and Economics (*PRIME*) model was used to examine the cost-effectiveness of *9vHPV* vaccine introduction to prevent *HPV* infection. Academic literature and anecdotal evidence were included on the demographic variables, cervical cancer incidence and mortality, treatment costs, and vaccine delivery costs. The incremental cost-effectiveness ratios (*ICERs*) were measured per disability-adjusted life years (*DALYs*) averted, using the heuristic cost-effectiveness threshold defined by the World Health Organisation (*WHO*). Analyses and data from international agencies were used in scenario analysis from the health system and societal perspectives.

Results

The 9vHPV vaccination was estimated to prevent 113 new cases of cervical cancer (discounted) during a 20-year period. From the health system and societal perspectives, the 9vHPV vaccination was very cost-effective in comparison with the status quo, with an ICER of A$47,008 and A$44,678 per *DALY* averted, respectively, using the heuristic cost-

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effectiveness threshold level. Considering delivery strategies, the *ICERs* per *DALY* averted were A$47,605, A$46,682, and A$46,738 for school, health facilities, and outreach-based vaccination programs from the health system perspective, wherein, from the societal perspective, the *ICERs* per *DALY* averted were A$46,378, A$43,729, A$43,930, respectively. All estimates of *ICERs* fell below the threshold level (A$73,267).

Conclusions

This cost-effectiveness evaluation suggests that the routine two-dose *9vHPV* vaccination strategy of preadolescent girls against *HPV* is very cost-effective in Australia from both the health system and societal perspectives. If equally priced, the *9vHPV* option is the most economically viable vaccine. Overall, this analysis seeks to contribute to an evidence-based recommendation about the new *9vHPV* vaccination in the national immunisation program in Australia.

Introduction

Cervical cancer is both a leading cancer and the leading cause of cancer deaths in women globally [1]. An estimated 570,000 new cases of cervical cancer were diagnosed in 2018, composing 6.6% of all cancers in women [1]. In Australia, over the last couple of years, the age-specific cervical cancer incidence has slightly reduced to 7.1 cases per 100,000 females in 2018 from 7.4 cases per 100,000 females in 2014 [2]. However, the incidence is quite high among young adult females at 15.0 cases per 100,000 females and was the most frequently diagnosed cancer among women in 2018 [2]. Persistent infections with human papillomavirus (*HPV*) are a key cause of cervical cancer and an established carcinogen of cervical cancer [3]. *HPV* is predominantly transmitted to reproductive-aged women through sexual contact [4]. Most HPV infections are transient and can be cleared up within a short duration, usually a few months after their acquisition. However, *HPV* infections can continue and evolve in cancer in some cases. There are more than 100 types of *HPV* infections that have been identified and divided into low- and high-risk types develop into cervical cancer [5]. Thirteen high-risk HPV types are known to be predominantly responsible for malignant and premalignant lesions of the anogenital area [6] and are the leading causes of most aggressive cervical cancers [7]. Further, *HPV* is also responsible for the majority of anogenital cervical cancers such as anal cancers (88%), vulvar cancers (43%), invasive vaginal carcinomas (70%), and all penile cancers (50%) globally [5]. The incidence of neck and head cancers caused by *HPV* infection is low but not negligible [8]. Cervical cancer is preventable through implementation of a primary prevention strategy such as vaccination worldwide including Australia [9,10]. Therefore, a reduction in cervical cancer incidence and associated cancer mortality along with the improvement of survival rates have the potential to reduce the burden of cervical cancer.

The high burden of cervical cancer in terms of incidence and associated mortality rates across the world could be reduced by incorporating a comprehensive primary prevention mechanism. Prevention mechanisms includes early vaccination, diagnosis, effective screening, adequate referral and advanced course of treatment procedures. In this context, *HPV* vaccinations (i.e., *bivalent and quadrivalent*) has been introduced in many countries in the past decade [10]. Currently, available *HPV* vaccines can promote herd immunity against cancer-causing types of *HPV* that helps to reduce the high-risk of cervical cancer burden. These vaccines have

played a significant role in preventing *HPV* infection types 16 and 18 [10], which cause more than 70% of cervical cancers in Australia [7].

Australia was the first country to implement a publicly-funded National *HPV* Immunisation Program (*NHIP*), starting with preadolescent girls in 2007, using the quadrivalent Gardasil® vaccine (*4vHPV*; Merck & Co., Kenilworth, NJ, USA) [11]. The goals of the immunisation program were to reduce the acquisition and spread of *HPV* infections and to achieve optimum coverage through the school-based delivery system [12]. This program for adolescent employed a three-dose schedule of the 4vHPV vaccine [13]. The *4vHPV* vaccine provides protection against *HPV* infection types 6, 11, 16, and 18 [14]. In the context of Australia, the *4vHPV* vaccine was replaced by the two-dose nonavalent Gardasil®-9 vaccine (*9vHPV*; Merck Sharp & Dohme) in 2018 [15]. According to the underlying distribution of *HPV* infection types of cervical cancers, the *9vHPV* vaccine builds population-level strong immunity against *HPV*-6, 11, 16, 18, 31, 33, 45, 52, and 58 infections [6] that cumulatively contribute to approximately 89% of all cervical cancers globally [16] and 93% in Australia [17]. Considering the primary prevention of *HPV* infection, the *9vHPV* vaccine is anticipated to reduce by 10% more the lifetime risk of diagnosis of cervical cancer in immunised cohorts than the *4vHPV* vaccine and by 52% more compared to non-vaccinated cohorts [18].

With the availability of vaccines against the different *HPV* infection types, there are good opportunities for primary prevention to add to continuing efforts on secondary prevention strategies. However, the decision for any country to add a new vaccine to national immunization programs requires careful assessment of the relative value of the vaccine compared with alternative uses of the required resources (i.e., cost-effectiveness) and its affordability (i.e., budgetary impact). Cost-effectiveness analysis (*CEA*) is a pragmatic approach which aims to examine the outcomes and costs of interventions or programs designed to improve health. *CEA* evolves measuring the net or incremental costs and effects of an intervention or program in terms of costs and health outcomes as compared with some comparator. There is considerable evidence of assessing the cost-effectiveness of the *9vHPV* vaccine in different country settings. In Canada, the *9vHPV* was found to be highly cost-effective compared with the *4vHPV* vaccine taking into consideration the shorter duration of protection (*9vHPV* = 20 years vs. *4vHPV* = lifelong), along with a lower vaccine efficacy (85% vs. 95%) [19]. In other studies conducted in the United States (*US*), the *9vHPV* vaccine was also found to be very cost-effective compared to the *4vHPV* vaccine [20]. However, findings from cost-effective evaluations will differ based on study settings, funding, perspectives and coverage of vaccination For example, in the *US*, Chesson et al. (2016) found that the *9vHPV* vaccine was not cost-effective, with an incremental cost-effectiveness ratio (*ICER*) of $146,200 per quality-adjusted life year (*QALY*) gained that exceeded the cost-effectiveness threshold ($100,000) [21]. Some cost-effective evaluations were performed using the same vaccine (i.e., 9-valent) in the *US* to capture the different dimensions of its economic viability [22–27]. These studies incorporated different study participants, designs, perspectives, vaccine delivery routes and model specifications. Simms et al. (2016) evaluated the *9vHPV* vaccine in a primary *HPV* screening scenario in both Australia and Canada [18]. They found that *9vHPV* had a significant impact on reducing cervical cancer incidence from the health system perspective. Further, they claimed that the incremental cost per dose in girls should not exceed a median of A$35.99. However, this study emphasised the impact of vaccines to prevent cervical cancer rather than their economic viability. Sufficient evidence did not arise for health policymakers to use the findings to develop cost-effective intervention strategies. In Germany, universal immunisation with *9vHPV* was suggested as it had an *ICER* of €22,987/*QALY* gained, which was below the threshold [28]. In Spain, a recent study evaluated a vaccine program in adolescent girls, wherein the *9vHPV* vaccine was found to be more highly cost-effective, with an *ICER* of €7,718 per *QALY* compared to the *4vHPV*

vaccine [29]. In the African setting, in Kenya and Uganda, a study recommended that the *9vHPV* vaccine was very cost-effective in both countries, wherein the additional cost of the *9vHPV* vaccine did not exceed I$8.3 per immunised girl [30].

In Australia, the *9vHPV* vaccine was introduced in 2018. There is limited current comprehensive evidence about the cost-effectiveness of the *9vHPV* vaccine in Australia across delivery strategies (e.g., school-based, health facility-based and outreach-based) from the health system and societal perspectives. The present study evaluates the cost-effectiveness of the *9vHPV* vaccine from both health system and societal perspectives across three delivery routes. However, the previous cost-effective evaluation considered only one perspective nor health system or societal, or both perspectives along with single vaccine delivery route. Further, the findings of the present study will provide evidence about the cost-effectiveness of the *9vHPV* vaccine to policymakers. These cost-effectiveness findings will also be significant for determining the optimal pricing of delivery strategies in the vaccination program in order to maximise the societal benefits of the introduction of the new *9vHPV* vaccine to Australia.

The objectives of this study are (1) to examine the cost-effectiveness of the *9vHPV* vaccine by considering three different vaccine delivery strategies in the setting of Australia from the health system and societal perspectives and (2) compare the *ICER* per case, disability-adjusted life years (*DALYs*), and life-years saved across delivery strategies such as school-based, health facility-based, and outreach-based programs.

Materials and methods

Study perspective

This study was designed from both the health system and societal perspectives. The societal perspective refers to all types of costs that can be identified, quantified, estimated, and valued no matter who incurred them and it is considered to be the summation of both provider and household costs. This is the recommended standard for undertaking cost-effectiveness analysis [31].

Model overview

The study used the Papillomavirus Rapid Interface for Modelling and Economics (*PRIME*) model. *PRIME* is a user-friendly model designed and developed by the World Health Organisation (*WHO*) in collaboration with the Johns Hopkins Bloomberg School of Public Health in Baltimore, the School of Hygiene and Tropical Medicine in London, and the Universite Laval in Quebec [10]. *PRIME* is a Microsoft Excel based (Microsoft Corp., Armonk, NY, USA) static model that measures the health and economic effects of the vaccination of adolescent girls against *HPV* infection. It is not designed to examine other dimensions, such as immunised males or older women or the impact of cervical cancer screening services [10]. Several spreadsheets are contained in this model to input different parameter-level data on demographics, an age-dependent incidence of cervical cancer, associated mortality, vaccine efficacy, vaccine coverage, and associated costs (e.g., vaccination costs, treatment costs). This model does not consider indirect effects like herd immunity.

Methodological assumptions

Methodological assumptions follow the *WHO* guidelines for cost-effectiveness analysis [32]. The use of cost-effectiveness analysis is recommended when considering health system and societal perspectives. In the context of the health system perspective, the average cost parameters associated with treating a woman with cervical cancer (per episode, over the lifetime), and the cost of the *HPV* vaccination program were both considered. From the societal viewpoint,

both direct medical (e.g., drugs, diagnostics) and non-medical (e.g., transportation) costs as well as indirect costs (e.g., productivity loses or income loss due to cervical cancer) were considered in the analysis. All future costs and health benefits were adjusted by a discount rate of 5% annually [5,29,32], which was validated in the sensitivity analysis. The primary outcome measure is the *ICERs* per *DALYs* averted. *DALY* estimation was undertaken by summing up the fatal burden (years of life lost; *YLL*) due to premature cervical cancer related mortality and the non-fatal burden (years lost due to disability; *YLD*) for patients surviving the condition.

$$DALY = YLL + YLD \tag{1}$$

$$YLL = \frac{N}{r}\left(1 - e^{-rL}\right) \tag{2}$$

$$YLD = I \times DW \times L\left(\frac{1 - e^{-rL}}{r}\right) \tag{3}$$

where, N = number of deaths; L (*YLL*) = standard life expectancy at the age of death in that year; I = number of people with cervical cancer cases; *DW* = disability weight; r = discount rate; and L (*YLD*) = duration of disability in years.

Cost-effectiveness analysis

The performance of competing strategies was explained using the *ICER* which were calculated by dividing the difference in cost with and without HPV vaccination by the difference in health outcomes (e.g., the number of *DALYs* averted, the number of deaths and cases averted) with and without vaccination in Australia. The *ICER* is used to examine whether the *9vHPV* vaccine is economically viable in Australia. In the context of Australia, no explicit cost-effectiveness threshold has been approved [33,34], although research has confirmed that there is a correlation between the incremental cost per health outcomes (e.g., *QALY* gained or *DALY* averted) and the probability of rejection of a health intervention or a new medicine [35]. The pharmaceutical industry claim that an acceptable threshold was in the range of *AUD* 45,000 to *AUD* 60,000 per additional *QALY* gained [36]. Some studies also stated that "Pharmaceutical Benefits Advisory Committee (*PBAC*) decisions in the past have shown that the *ICER* per *QALY* gained was of the order of $50,000" [18,37]. The present study intended to evaluate the cost-effectiveness of the *9vHPV* vaccine in terms of the *ICER* per *DALYs* averted. Further, *DALYs* and *QALYs* differ in concept and application. The concept of *DALYs* was used to measure the disease burden using life lost due to premature death and the time spent in worse healthy states. Empirical evidence in the Australian context is limited to the use of the willingness-to-pay (*WTP*) threshold values for the *ICER* per *DALYs* averted. In reporting the cost-effectiveness scenario, the present study used the heuristic cost-effectiveness threshold as defined by the *WHO* Commission on Macroeconomics and Health (*CMH*) [38]. The gross domestic product (*GDP*)-related cost-effectiveness thresholds were based on assumptions about leisure time, non-health consumption, longevity and health-related quality of life. An intervention is cost-effective if the *ICER* per *DALY* averted is less than three times of a country's annual per capita GDP. According to this guideline, the *CMH* recommended three broad decision rules, as follows: (1) a program or intervention is defined as very cost-effective if the *ICER* per *DALY* averted is less than one time the *GDP* per capita; (2) a program or intervention is cost-effective if the *ICER* per *DALY* averted is one or more times the *GDP* per capita but less than or equal to three times the *GDP* per capita; and (3) a program or intervention is not cost-effective if the *ICER* per *DALY* averted is more than three times the *GDP* per capita [31].

Vaccine and efficacy

The Australian Technical Advisory Group on Immunisation (*ATAGI*) in 2018 advised moving from using the quadrivalent *4vHPV* to using the nonavalent Gardasil-9 (*9vHPV*) vaccine [39]. The *9vHPV* vaccine has been registered for use in Australia [40]. The vaccine is funded through the national immunisation program (*NIP*) and delivered primarily by state and territory school-based immunisation programs in Australia [39]. This vaccine is manufactured using a procedure similar to that of the *4vHPV* vaccine, which contains 0.5mg of aluminium hydroxyphosphate sulphate and a yeast expression system [40]. The *4vHPV* vaccine contains five more virus-like particles than the original vaccine, identical to those in the protective capsule around the nine included strains (*HPV*-6, 11, 16, 18, 31, 33, 45, 52, and 58) with the aim to further reduce the *HPV* disease burden. The high prophylactic efficacy of the *9vHPV* vaccine (93%) against *HPV* infection is evident both in Australia (77% for *HPV* types 16, 18 and 16% for *HPV* types 6, 31, 33, 45, 52, 58) [17] and globally (89%) [16]. However, no herd immunity was considered. It was recommended for the target cohort of adolescents aged 12 years to receive a two-dose *9vHPV* vaccination for several reasons [39]. First, administering a vaccination at this age is more likely to ensure it is being given before their first sexual encounter (and *HPV* exposure). Also, the immune response tends to be stronger and more long-lasting when the vaccine is given to pre-adolescents. However, *9vHPV* is not recommended for use during pregnancy. Similarly, vaccination is delayed if the person is unwell or has a high temperature, medical advice is recommended if the person is allergic to yeast or has had a severe reaction to a previous vaccine, and anyone who receives the vaccine is recommended to sit for 15 minutes thereafter to reduce the risk of fainting.

Vaccine delivery strategies

The *HPV* vaccine delivery strategy is an important aspect that needs to be considered carefully by each country. According to the country-specific context, the costs of vaccine delivery may vary. The *WHO* has recommended several types of common vaccine delivery strategies for different country settings. One example is vaccine delivery at healthcare facilities and via outreach routes (e.g. school-based program) and campaigns. It may be required to use a combined vaccine delivery strategy to ensure access among the entire target population. The *9vHPV* vaccine has been delivered in Australia through school-based *NIP* in all states and territories to the target population cohort of school-going adolescents since January 2018. Two doses of *9vHPV* are recommended to be administered at a minimum interval of six to 12 months between doses [39]. In some cases, general practitioner (*GP*) and other primary health care providers are generally engaged to catch up doses missed in the routinely school-based *NIP*. All providers are proactively involved in delivering and ensuring the completion of all doses of the *9vHPV* vaccine to those individuals with special requirements, vaccine hesitancy, or immunocompromise. However, individuals who have already been fully immunised with HPV vaccines are not eligible for free *9vHPV* vaccination. The present study incorporated another two hypothetical vaccine delivery strategies, as health facility-based and outreach-based, both from the health system and societal perspectives.

Vaccine delivery costs

The present study considered vaccine delivery related costs across three delivery strategies (e.g., school-based, health facility-based and outreach-based). Costs were derived from an existing costing study [41]. This study captured both financial and economic costs according to the *WHO* guidelines [42], included eight cost parameters, and focused on the investment and recurrent cost impacts of *HPV* vaccination on existing vaccination services. Furthermore,

the investment costs were defined as microplanning (e.g., per diems and travel allowances, venue rental, transport and personnel time spent), training (e.g., training materials, stationery), social mobilisation (e.g., facilitator time in meetings, production of television/radio spots, posters, leaflets, value of teacher and volunteer time), and cold chain supplement. In addition, recurrent costs were covered including vaccines, service delivery, monitoring and evaluation, and waste disposal.

Cervical cancer treatment costs

Direct medical costs. Cervical cancer treatment costs were derived from a previous cost-of-illness study considering four treatment procedures: localised cancer treatment, regional cancer treatment, distant cancer treatment and terminal care [43]. The treatment costs were estimated based on different parameters such as surgical (e.g., conisation, hysterectomy, radical hysterectomy) and non-surgical (e.g., radiation therapy, adjuvant radiation therapy, chemo-radiation) [43]. Different types of activities included in cancer diagnosis were the direct medical costs such as colposcopy, chest X-ray, computerised tomography scan, positron-emission tomography scan, magnetic resonance imaging, bone scan and cystoscopy. Other costs included those related to inpatient care, emergency care, medicine costs, rehab, complex continuing care, long-term care, home care services, physician consultations, and non-physician provider costs.

Indirect costs. Indirect costs of cervical cancer patients and vaccine receivers were restricted to the loss of labour productivity due to ill health. Absenteeism-related data were obtained for a cervical cancer episode from elsewhere [32]. Other indirect costs were estimated using the human capital approach (S1 Table). The production losses were measured in both monetary and quantitative terms (e.g., days of productivity loss) [44]. The value of unpaid time devoted to own care and family defined caregivers [45]. The value of daily productivity was measured based on an age-specific average wage [46]. The average daily wage of cervical cancer patients were used for adult patients, and one-half of that wage was applied to teenager patients. Intangible costs related to pain, discomfort and grief were excluded [46]. All costs were converted into 2018 Australian dollars using the Consumer Price Index of Health Care [47].

Dynamic modelling of HPV transmission and the impact of vaccination. A dynamic cancer disease model was introduced to cover *HPV* transmission, *HPV* vaccination and cervical pre-cancer (Fig 1). The model incorporates demographics, economics, *HPV* attributable fractions in cervical cancer and vaccine uptake assumptions, as detailed in Table 1. When modelling the impact of *HPV* vaccination, the model captured the effects of herd protection (i.e., naturally acquired immunity) on the unvaccinated cohort. It was assumed that *9vHPV* vaccine type-specific (*HPV* types) efficacy in girls was 100% and that the duration of protection was 20 years [19,27].

Sensitivity analysis. A deterministic sensitivity analysis was performed to examine the robustness of the results. The output estimates varied for each value of the input parameters. These prices were derived from the academic and anecdotal literature and aimed to determine the impact of uncertainty in input assumptions on the *ICERs*.

Results

Model input parameters

Table 1 shows several input parameters, including the population cohort at birth, coverage of full dose vaccine, vaccine effectiveness versus *HPV*-9 types, the price of vaccine, and vaccine delivery costs per fully immunised girl. Cervical cancer treatment related costs per episode

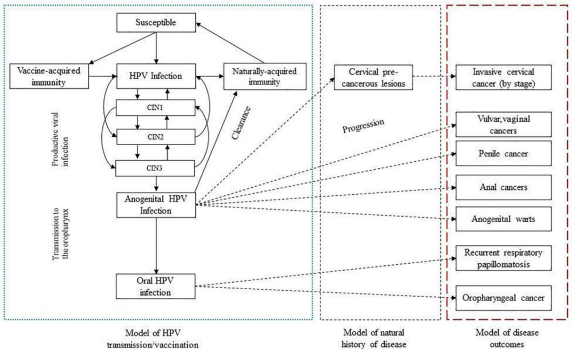

Fig 1. Simplified diagram of the model of HPV transmission, human impact of vaccination and disease outcomes in Australia.

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included direct costs (e.g., medical and non-medical costs) and indirect costs (e.g., loss of labour productivity for patients and caregivers during treatment). *DALYs* incurred for nonfatal and fatal cervical cancer episodes, and epidemiological data related to cervical cancer incidence were used. The sizes of the female birth cohort and the cohort at immunisation age were 191,340 and 118,679, respectively. Vaccination coverage was 86%, whereas vaccine effectiveness against *HPV* infections was 95%. The price of the vaccine and direct and indirect vaccine delivery costs were A$280, A$31.77, and A$17.59, respectively. Cervical cancer treatment costs were A$61,272, wherein 53.78% (A$32,952) were direct costs and 46.22% (A$28,322) indirect costs. These varied depending on the types of treatment and stages of cancer. Cervical cancer incidence and mortality-related data were extracted from national sources and the *GLOBOCAN*-2018 study [48]. Methodological assumptions such as disability weights (for cancer diagnosis, non-terminal and terminal) are shown in Table 1. Vaccine protection was considered to be 20 years as suggested by an expert panel and earlier research [49].

Cost-effectiveness estimates

The model estimates in Table 2 show the cost-effectiveness of the *9vHPV* vaccination in Australia under various assumptions about the cost of cervical cancer treatment and the cost of vaccination across delivery strategies. The *9vHPV* vaccination in Australia would cost the public approximately A$28.11 million for this target population cohort, although several types of treatment procedures would be transferred from the health system perspective and the value of A$26.72 million from a societal perspective across the various vaccine delivery strategies (e.g., school-based, health facility-based, outreach-based) would result. State and territory school-based immunisation programs primarily implement the *9vHPV* vaccination through the *NIP* in Australia. Another two possible delivery strategies (e.g., health facility-based and outreach-based) were also included for comparison. Overall, the *ICER* per *DALY* averted was A$47,008 from a health system perspective and A$44,678 from a societal perspective, respectively. Considering delivery strategies, the *ICERs* per *DALY* averted were A$47,605, $46,682 and $46,738 for school-based, health facility-based and outreach-based programs, respectively, from the health system perspective. Whereas, from the societal perspective, the values were A $46,378, A$43,729, and A$43,930 respectively. Both perspectives for *ICERs* per *DALY* averted fell below the 2018 fiscal year *GDP* per capita in Australia (A$73,267), which is used as a

Table 1. Input parameter assumptions and sensitivity analysis.

Input parameters	Health system perspective				Societal perspective				Sensitivity analysis and potential sources
	Overall	School-based	Health facilities-based	Outreach-based	Overall	School-based	Health facilities-based	Outreach-based	
Population									
Population cohort at birth (female) ('000)	191.34	191.34	191.34	191.34	191.34	191.34	191.34	191.34	[50]
Population cohort at vaccination age (female) ('000)	118.68	118.68	118.68	118.68	118.68	118.68	118.68	118.68	[40,51]
Target age group (yrs)	12	12	12	12	12	12	12	12	[39]
Vaccination and vaccine delivery costs									
Vaccination coverage (full doses)	86%	86%	86%	86%	86%	86%	86%	86%	72.00% -90.1% [51–55]
Vaccine effectiveness vs HPV types[1]	95%	95%	95%	95%	95%	95%	95%	95%	85% -100% [25,52,53,56]
Price of vaccine per fully immunised girl (*FIG*) (A$)	280	280	280	280	280	280	280	280	270–320 [32,41,57]
Direct costs of vaccine delivery per *FIG* (A$)	31.77	35.27	29.86	30.19	31.77	35.27	29.86	30.19	[5,32,41]
Indirect costs of vaccine delivery per *FIG* (A$)	-	-	-	-	17.59	24.05	13.93	14.79	
Total cost of vaccine delivery cost per *FIG* (A$)	31.77	35.27	29.86	30.19	49.36	59.32	43.80	44.98	
Total costs of vaccination per *FIG* (A$)	311.77	315.27	309.86	310.19	329.36	339.32	323.80	324.98	300–500 [5,32,41]
Treatment cost per episode									
Direct costs A$ ('000)	32.95	32.95	32.95	32.95	32.95	32.95	32.95	32.95	[32,43]
Indirect costs (including caregiver costs) A$ ('000)	-	-	-	-	28.32	28.32	28.32	28.32	[32,43]
Total treatment costs A$ ('000)	32.95	32.95	32.95	32.95	61.27	61.27	61.27	61.27	36.05–71.05 [32,43]
Methodological assumptions									
Disability weight for cancer diagnosis	0.09	0.09	0.09	0.09	0.07	0.09	0.09	0.09	0.061–0.095 [10,32,58,59]
Disability weight for non-terminal (per year)	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.065–0.091 [10,32]
Disability weight for terminal cancer	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.70–0.90 (assumption)
Vaccine protection (years)	20 yrs	20 yrs	20 yrs	20 yrs	20 yrs	20 yrs	20 yrs	20 yrs	20 years [19]
Discount rate	5.0%	5.0%	5.0%	5.0%	5.0%	5.0%	5.0%	5.0%	3.0% -5.0% [23,24,30,32,58,60]
Proportion of cervical cancer cases that are due to [1]*HPV*-types	90.3%	90.3%	90.3%	90.3%	90.3%	90.3%	90.3%	90.3%	70% -95.0% [9,15,17,39]
Economic growth									
GDP per capita, A$	73,267	73,267	73,267	73,267	73,267	73,267	73,267	73,267	73,267 [61]

[1]HPV-6, 11, 16,18,31,33,45,52,58

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threshold for examining the cost-effectiveness of an intervention. Similarly, consistent results were presented for the *ICERs* per life-year saved for both perspectives across delivery strategies (Table 2). This evaluation signifies the cost-effectiveness of the *9vHPV* vaccination from both perspectives in Australia.

Table 2. Outcomes of the vaccination program*.

Scenario	Scenario– 1				Scenario—2			
Perspective	Health system perspective				Societal perspective			
Vaccine delivery strategies	Overall	School-based	Health facilities-based	Outreach-based	Overall	School-based	Health facilities-based	Outreach-based
Output parameters								
Cohort size at birth (female), ('000)	191.34	191.34	191.34	191.34	191.34	191.34	191.34	191.34
Cohort size at vaccination age (female) ('000)	118.68	118.68	118.68	118.68	118.68	118.68	118.68	118.68
Total costs of vaccination, A$ ('000)	31,820.48	32,177.70	31,625.53	31,659.21	33,615.78	34,632.34	33,048.30	33,168.74
Total treatment costs averted, A$ ('000)	3,709.75	3,709.75	3,709.75	3,709.75	6,898.41	6,898.41	6,898.41	6,898.41
Net costs of the vaccination, A$ ('000)	28,110.73	28,467.95	27,915.78	27,949.47	26,717.37	27,733.93	26,149.90	26,270.33
Number of averted-								
- Cervical cancers case averted	113	113	113	113	113	113	113	113
- Deaths averted	23	23	23	23	23	23	23	23
- Life years saved	543	543	543	543	543	543	543	543
Nonfatal *DALYs* averted	55	55	55	55	55	55	55	55
Incremental cost-effectiveness ratio (*ICER*) per-								
- Cervical cancers case averted, A$	248,767	251,929	247,042	247,340	236,437	245,433	231,415	232,481
- Life saved, A$	1,222,205	1,237,737	1,213,730	1,215,194	1,161,625	1,205,823	1,136,952	1,142,188
- Life year saved[1], A$	51,769	52,427	51,410	51,472	49,203	51,075	48,158	48,380
- *DALYs* averted[1], A$	47,008	47,605	46,682	46,738	44,678	46,378	43,729	43,930
Cost-effectiveness threshold								
GDP per capita, A$	73,267	73,267	73,267	73,267	73,267	73,267	73,267	73,267
Decision rules								
- Very cost-effective[1]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
- Cost-effective[2]								
- No cost-effective[3]								

[1]Very cost-effective if *ICER* per *DALYs* averted $<$ 1 time *GDP* per capita

[2]cost-effective if *ICER* per *DALYs* averted $\geq$ 1 times *GDP* per capita and $\leq$ 3 times *GDP* per capita

[3]no cost-effective if *ICER* per *DALYs* averted $>$ 3 times *GDP* per capita.

*Costs and *DALYs* were discounted at 5% per year.

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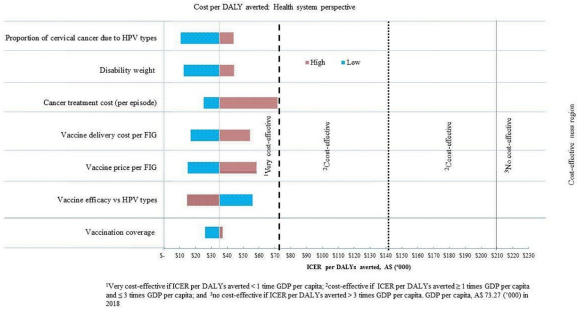

Fig 2. Changes in input model parameters on ICER per DALY averted from a health system perspective.

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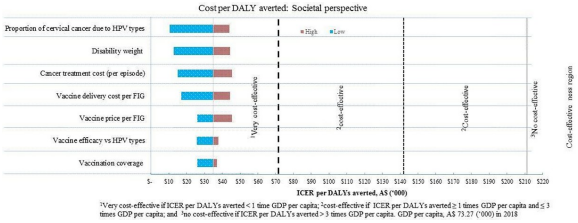

Fig 3. Changes in input model parameters on ICER per DALY averted from a societal perspective.

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Sensitivity analysis

Model uncertainty was investigated by changing the values of input parameters in the cost-effectiveness model from the health system (Fig 2) and societal perspectives (Fig 3). The output of the deterministic sensitivity analysis showed that the price of vaccine, vaccine delivery costs, the incidence of cervical cancer, vaccination coverage, vaccine efficacy, and cervical cancer treatment costs were the dominating parameters that influence the *ICERs* per *DALY* averted. These findings are conservative, as only a simple static model of 9vHPV vaccination was considered. According to the *WHO-CHOICE* threshold, the *9vHPV* vaccination is a very cost-effective and favourable option for introduction in Australia. This analysis indicates that the model outputs are robust to variation in the values of all parameters; however, there is a necessity to confirm that the pricing of the vaccine is appropriate in the context of Australia.

Discussion

The present study is a comprehensive cost-effectiveness evaluation of the introduction of a *NIP* with the new *9vHPV* vaccine to adolescent girls in Australia. The impact of *9vHPV* vaccination on health and economic outcomes was measured using various model scenarios allowing for the testing of three different vaccine delivery strategies.

The findings show that the new 9-valent vaccination of 12-year-old adolescent girls is highly cost-effective, with *ICERs* per *DALY* of A$47,008 and A$44,678, from the health system and societal perspectives, respectively. Although the *9vHPV* vaccination has been implemented as part of the school-based delivery strategy, the present study has emphasised two other hypothetical delivery strategies, namely health facility-based and outreach-based programs. If the *9vHPV* vaccination program is extended to these delivery outlets, the *ICER* remains highly cost-effective at A$46,682/*DALY* averted for health facility-based and A$46,738/*DALY* averted for outreach-based vaccination programs compared with a school-based vaccination program (*ICER* = A$47,605/*DALY* averted). Considering the societal perspective, the *9vHPV* vaccination also reports a very cost-effective outcome, with an *ICER* of A$46,378/*DALY* averted, A $43,729/*DALY* averted, and A$43,930/*DALY* averted for the school-based, health facility-based and outreach-based vaccination programs, respectively. It is noteworthy that the *ICERs* are comparatively lower from the societal perspective in terms of vaccine delivery strategies compared with the health system perspective.

Immunisation would still be very cost-effective from both the health system and societal perspectives if the program is extended to encompass other delivery strategies. However, no herd immunity was considered in the context of these strategies. This evaluation provides a piece of initial evidence for the value of money of investments in the *9vHPV* vaccination and protection against transient and persistent infections of *HPV*. Under the input model

assumptions, the present evaluation of the two-dose *9vHPV* vaccination would be very cost-effective across delivery strategies. From the societal perspective, the *ICER* per *DALYs* averted was comparatively lower than the health system perspective in terms of delivery strategies. The cost-effectiveness evaluation is significant even allowing for different vaccine delivery strategies and vaccination model assumptions.

This study findings are consistent with the conclusions from the evaluation of cost-effectiveness of the *9vHPV* vaccination in other country settings including Austria [62], Canada [19], Germany [28], Italy [5], Kenya and Uganda [30], South Africa [52], and the *US* [21,63]. These studies estimated that an immunisation programs with the *9vHPV* vaccine was likely to belong within an acceptance heuristic threshold level of cost-effectiveness or even reach cost-saving status in different country settings. In Canada, the *9vHPV* vaccine was offered to school-aged girls and evidenced to be cost-effective at a price increment lower than CAN$24 [19]. Further, *9vHPV* was found to be cost-effective in the *US*, if the incremental cost per dose of the *9vHPV* was less than US$13 for a gender-neutral strategy (school-aged girls only) from a health system perspective [64]. From a societal perspective, the *9vHPV* vaccine would also be considered very cost-effective at the national and state levels in the *US* if the vaccine price of *9vHPV* was US$148 per dose (in 2016) [65], whereas two-dose schedules of the *9vHPV* vaccine were likely more cost-efficient compared with three-dose schedules considering the population-level effectiveness [18]. Another recent study showed that introducing a universal *9vHPV* vaccination in Germany would yield noteworthy incremental public health benefits and be highly cost-effective [28].

The present evaluation was performed among school-aged preadolescent girls (i.e., 12 years of age). Previous studies confirmed that vaccination of girls only was commonly more effective versus vaccination of both genders in different settings [28,32]. The two-dose *9vHPV* vaccination approach is recommended for the target cohort of adolescent girls aged 12 to 14 years for several reasons [39]. Giving the vaccination at this age is likely to ensure immunization before their first sexual encounter and *HPV* exposure. As a result, the immune response tends to be stronger and more long-lasting when the vaccine is present in preadolescent girls. A vaccination schedule against *HPV* would allow for a more efficient primary strategy by protecting females exposed to male partners and unvaccinated females to prevent *HPV* transmission [9,28,63]. Eventually it would provide additional benefits to potentially accomplish virus eradication [28].

Most previous studies pay little attention to comparing the cost-effectiveness from the health system and societal point of views across vaccine delivery strategies. Thus, the evidence produced is not sufficient for health policymakers to decide upon effective or conclusive strategies. This study findings however provides effective and efficient empirical evidence of its economic viability. Health policymakers can use this evidence for the allocation of health resources and extend their vaccination program to other country settings to ensure optimal health gains.

This study has some strengths that should be highlighted. This vaccination is justified overall by epidemiological and health and economic outcomes. Under the input model assumptions, this study demonstrates that the *9vHPV* vaccination is economically viable from both the health system and societal perspectives. A broader societal perspective calculates additional benefits of the new vaccine that are mainly associated with reduced productivity losses. *HPV*-related cervical lesions lead to a loss or reduction of women's household income due to high productivity loss (presenteeism) and absenteeism [66]. Ultimately, *HPV* related diseases lead to a decrease in a victim's socioeconomic position, which is costly for working women, their employers, and the economy. The study findings show distinctly that three vaccine delivery strategies (e.g., school-based, health facilities and outreach-based) are cost-effective. This is

significant for health policymakers, strategic leaders, health scientists, cancer experts and public health professionals to help promote further implementation and extension of vaccination via a universal immunisation strategy.

This study also has some caveats. Little evidence is available on the health and economic burden of cervical cancer in Australia. Some of the model parameters related to indirect costs for cervical cancer treatment and costs of vaccination across vaccine delivery strategies (e.g., school-based, health facility-based, and outreach-based) are not available for Australia. Indirect costs of patients (e.g., opportunity costs) in terms of absenteeism due to cervical cancer and caregiver time were taken from the academic literature and anecdotal evidence in Australia and international sources. In this context, the cost-of-illness study would be appropriate for measuring the productivity losses of patients and their caregivers. However, due to a limited timeframe it was not able to conduct a cost-of-illness study among cervical cancer patients. It was presumed that the *9vHPV* vaccine would be delivered to both boys and girls, but that it would only be cost-effective among girls, as the direct health impacts for *9vHPV* is expected to be small for boys. This study used the *GDP* per capita thresholds level as defined by *CMH*. The *GDP* threshold might be a suitable screening method but should not be the only consideration for vaccination investment as there are other issues such as feasibility, affordability, alternative interventions and other local considerations which are not accounted for in the threshold level decision rule. Finally, the study findings were generated for the national context in Australia and might vary by state or regional settings, depending on cervical cancer outcomes (e.g., incidence, mortality), treatment procedures, cancer stages, costs of vaccination, and coverage of immunisation.

Conclusions

This study is an extensive cost-effectiveness analysis of *9vHPV* vaccination in Australia from both the health system and societal perspectives. The introduction of the *9vHPV* immunisation is assessed to be very cost-effective from both perspectives. It incorporated three delivery strategies (school-based, health facility-based, and outreach-based). However, this high-value vaccination would need substantial upfront investments. Considering a two-dose schedule, the *9vHPV* vaccination demonstrated 'good value for money', if the vaccination could accomplish a high vaccination coverage and provide protection. The findings of this evaluation contribute to decision-making about the incorporation of the *9vHPV* vaccine into a universal cervical cancer vaccination program in Australia. With continued assessment of the potential vaccine properties as well as vaccine delivery and scale-up strategies, the two-dose *9vHPV* vaccine would provide significant health and economic benefits for preadolescents and society. Finally, the success of *9vHPV* vaccination will be contingent on several predominating factors including value for money, feasibility, acceptability, and affordability.

Supporting information

S1 Table. Cost analysis.
(XLSX)

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Chapter-3: Conclusions

Chapter 3: Conclusions

This chapter is an overview of the findings of the thesis, together with suggestions to strengthen healthcare services, improve educational materials and general information given to cancer survivors. Future research scope and questions are also suggested. The advantages of adopting longitudinal design and health economics approaches, using a quantitative approach are discussed.

3.1 Introduction

A longitudinal and health economics perspectives-based, quantitative study of the cancer burden and economic viability of cancer prevention strategy (cancer vaccination) has sought to investigate patient adverse experiences over extended periods of time. The findings from this thesis may assist medical/health and allied professionals and health policymakers to understand issues and concerns related to long-term cancer burden. Note also that these issues may not be static. Subsequent recommendations may help other individuals diagnosed with cancer in the future to make informed choices and to reduce the burdens they may suffer. The following discussion briefly highlights findings from each of the studies, presented in more detail in chapter 2, and then discusses them more generally.

3.2 Overview of the key findings from chapter 2 (Studies 1-5).

The major findings of the study are divided into three themes as follows:

3.2.1 Understanding the challenges of cancer outcomes (Study 1)

Cancer incidence (annual average percentage change, *AAPC* = 1.33%), hospitalisation (*AAPC* =1.27%), cancer-related mortality (*AAPC* = 0.76%), and burden of cancer (*AAPC* = 0.84%) all increased significantly over the period of 1982-2014. The same-day (*AAPC* = 1.35%) and overnight (*AAPC* = 1.19%) hospitalisation rates also showed an increasing trend. Furthermore, the ratio (least-most advantaged economic resources ratio, *LMR* of mortality) and (*LMR* of incidence) was especially high for cervix (M/I = 1.80), prostate (M/I = 1.51), melanoma (M/I = 1.33), Non-Hodgkin Lymphoma (M/I = 1.32) and breast (M/I =

1.31), suggesting that survival inequality was most pronounced for these cancers. In addition, people who lived in deprived socioeconomic status were more likely to bear an increasing cancer burden in terms of incidence, mortality and death.

3.2.2 Long-term health status burden, chronic comorbid conditions, productivity-related disability, and its consequences over the extended period (Studies 2-4)

A longitudinal health status burden of cancer survivors was prominent among this Australian sample (*Study 2*). Approximately 36% of cancer survivors had an initial extreme health status burden in 2013, while this had declined significantly (21%) by 2017. This was evidenced in significant improvements in body pain, social functioning, and mental health measures. Several individual-level factors, including an adequate level of physical activity, social support, and higher economic status, were significantly associated with improving health status. In contrast, factors that significantly determined increaseing health status burden included being unemployed, Indigenous, uninsured, and living in a regional location (*Study 2, Article II*).

However, the majority of cancer patients suffer from chronic diseases or comorbid conditions. In the case of cancer, chronic comorbidity refers to the existence of one or more additional conditions in a person simultaneously. The risk of having comorbidity increases during treatment as well as oncology follow-up periods (AIHW, 2018, 2019; WHO, 2018), which then adversely influences treatment choices and outcomes. Understanding more about comorbidities among cancer patients can generate possible evidence as well as provide direction for prevention, management, and treatment of chronic diseases. Concerning chronic comorbid conditions, 61% of cancer patients experienced at least one chronic disease over the oncology follow-up period, and 21% of patients experienced three or more chronic diseases (*Study 3, Article III*). Furthermore, a higher risk of chronic comorbid conditions was greatly evidenced with cancer patients aged 65 years or over, inadequate levels of physical activity, patients who suffered from an extreme or moderate health burden, and patients living in the poorest households. The importance of comorbidities in cancer patients draws from an increasing awareness

of their impacts on cancer care and outcomes. Chronic comorbid conditions of cancer patients contribute to a major clinical challenge in terms of long-term health conditions or illness (e.g., disability) (Stairmand et al., 2015).

Also, the burden of cancer imposes a long-term productivity-related disability that leads to an economic burden on the individual, family and society. Lost productivity, loss/reduction of household income, and increased expenditure due to illness resulting in reduced earnings and higher expenditure, which consequently lead to a decrease in their socioeconomic position. In Australia, 50% of cancer survivors suffer from a long-term productivity-related disability, amongst whom 18% of patients have experienced extreme level disability (*Study 4, Article IV*). In addition, the *magnitude* of disability levels increases significantly with the level of health burden. For instance, a cancer survivor who faces a severe health burden faces a 5.32 times higher risk of having a productivity-related disability compared with patients who have reported no health burden. The disability level is extended among patients who engage in an unhealthy lifestyle (e.g., inadequate levels of physical activities, those who drink alcohol or smoke tobacco).

3.2.3 Economic evaluation of cancer prevention program (cancer vaccination) (Study 5)

The World Health Organization (*WHO*) recommends that programs including cancer vaccination are recognised to be economically viable before implementation. With the availability of vaccines against the different *HPV* infection types, there are good opportunities for primary prevention to add to continuing efforts with secondary prevention strategies. However, the decision for any country to add a new vaccine to national immunization programs requires careful assessment of the relative value of the vaccine compared with alternative uses of the required resources (i.e., cost-effectiveness) and its affordability (i.e., budgetary impact). The *WHO* has recommended several types of common vaccine delivery strategies for different country settings. One example is vaccine delivery at healthcare facilities and via outreach routes (e.g. school-based program) and campaigns. A combined vaccine delivery strategy may be required to ensure access amongst the entire target

population. However, previous cost-effectiveness evaluations have considered only a health system or societal perspective in isolation, or both perspectives along with a single vaccine delivery route.

Despite some heterogeneity in approaches to measuring cost-effectiveness, ten studies concluded that *9vHPV* vaccination was cost-effective while two studies concluded that they were not (*Study 5; Article-V*). The addition of adolescent boys into an immunisation program was cost-effective when the vaccine price and coverage was comparatively low. When vaccination coverage for females was 75% or more, gender-neutral *HPV* vaccination was less cost-effective than when targeting only girls aged 9–18 years. A multi-cohort immunization approach was cost-effective in the age range of 9–14 years, but the upper age limit at which vaccination was no longer cost-effective needs to be further evaluated (*Study 5; Article-V*) within a global context.

In Australia, the *9vHPV* vaccination was estimated to prevent 113 new cases of cervical cancer (discounted) during a 20-year period (*Study 5, Article VI*). From health system and societal perspectives, the *9vHPV* vaccination was very cost-effective in comparison with the status quo, with an *ICER* of A$47,008 and A$44,678 per *DALY* averted, respectively, using the heuristic cost-effectiveness threshold level. Considering delivery strategies, the *ICERs* per *DALY* averted were A$47,605, A$46,682, and A$46,738 for school, health facilities, and outreach-based vaccination programs from the health system perspective, while from the societal perspective, the *ICERs* per *DALY* averted were A$46,378, A$43,729, A$43,930, respectively.

3.3 Limitations

Despite the compelling findings of this study, there are limitations. Due to the paucity of survival data, this study has not captured inequalities regarding cancer survivorship in detail (*Study 1*). However, there is limited understanding about what is driving the changes of cancer outcomes reported in this thesis, which may reflect random variation or changes in unknown risk factors, and therefore highlight the need for more research into the aetiology of cancer.

Study participants (*Study 2-4*) were derived from the *HILDA* survey, which covers the health, economic, employment, income and health characteristics of Australian household members aged 15 years and older. Children who suffered from cancer were not included in this study. This study considered the overall health status of cancer survivors, which might vary in terms of cancer stages and types of cancer. The authors were not able to measure the cancer-specific health status of cancer patients due to the paucity of available information. Examining the long-term health status burden, chronic comorbid conditions, and productivity-related disability is widely perceived to have substantial potential as an endpoint in health outcomes research; however, results are partially dependent upon study methods and outcome variables of interest. The participants of the present study (*Study 2-4*) were derived from the protocol "*HILDA* study" (Summerfield et al., 2018), and long-term health conditions of cancer patients might change for independent study designs as well as the application of survey instruments.

In the *HILDA* survey waves, the length of the survey period may have introduced uncontrolled bias, as changes in health status are not instantaneous and might emerge only after time, which was not captured in this study. Due to funding restrictions and the study's timeframe, this research did not consider cancer patients who registered for cancer surveillance as well as received health care services from health facilities (e.g., private clinics, community clinics, secondary or tertiary hospitals).

Due to the paucity of cancer-related data in the *HILDA* study, the researcher was unable to perform cancer-specific or period of treatment related calculations. Furthermore, the study findings were based on self-reported information that might have been impacted by respondents' prejudice (e.g., silence and over-response), or by problems in understanding and interpretation.

In *Study 5*, the economic evaluation of cancer vaccination (cost-effectiveness analysis) based on *GDP* thresholds of 1–3 times the *GDP* per capita, lacks country specificity and has little meaning for other country-level decision making (Bertram et al., 2016). It is uncertain whether this threshold truly reflects the country's affordability or societal willingness to pay for additional health gains. Additionally,

GDP was originally intended to measure the experience of people residing in urban areas and thus, it may not actually reflect the experience of the entire population in a country, especially those living in rural areas. Apart from an economic standpoint, other factors should be considered for the national immunization program, such as budget availability, political issues, cultural influences and availability of a healthcare workforce. Some of the model parameters (*Study 5, Article VI*) related to indirect costs for cervical cancer treatment and costs of vaccination across vaccine delivery strategies (e.g., school-based, health facility-based, and outreach-based) were not available for Australia. Indirect costs of patients (e.g., opportunity costs) in terms of absenteeism due to cervical cancer and caregiver time were taken from the academic literature and anecdotal evidence from Australia and international sources. In this context, a cost-of-illness study would be appropriate for measuring the productivity losses of patients and their caregivers. However, due to a limited timeframe it was not possible to conduct a cost-of-illness study among cervical cancer patients. It was presumed that the *9vHPV* vaccine would be delivered to both boys and girls, but that it would only be cost-effective amongst girls, as the direct health impacts for *9vHPV* is expected to be small for boys. This study used the *GDP* per capita thresholds level, as defined by the *WHO* Commission on Macroeconomics and Health. The *GDP* threshold might be a suitable screening method but should not be the only consideration for vaccination investment as there are other issues, such as feasibility, affordability, alternative interventions and other local considerations, which are not accounted for in the threshold level decision rule. Finally, the study's findings were generated for the national context of Australia and might vary by state or regional settings, depending on cervical cancer outcomes (e.g., incidence, mortality), treatment procedures, cancer stages, costs of vaccination, and coverage of immunisation.

3.4 Contribution of the thesis

This thesis contributes to the existing literature by providing first-hand evidence on the trends, determinants and inequalities of incidence, mortality and burden of cancer, using Australian nationally representative population-based data (2,784,148

registered cancer cases) over the past 33 years (*Study 1*). The study's findings also provide authorities with national evidence about the trends and magnitude of the inequalities in the cancer burden and hopefully assist in developing low-cost interventions to reduce this burden.

Considering the longitudinal perspective, these studies (*Study 2-4*) have proposed the development of a better understanding of long term follow-ups, and the application of well-validated and reliable longitudinal wave measures of the impacts of a cancer diagnosis on the long-term health status burden, chronic comorbid conditions and productivity-related disability of individuals over the 2003-2017 period. This study thus complements and contributes to this strand of ongoing cancer research to increase awareness and improve public health practice among sufferers and survivors, and to measure impact.

These findings will help to improve the understanding of potential employment opportunities after a cancer diagnosis. In addition, these findings may be considered from different perspectives in cancer policy discussions: the cancer survivor (e.g., health status burden, chronic comorbid conditions, productivity-related disability level and return to employment), the caregiver and the family (e.g., the health burden, reduction of socio-economic position and risk of poverty), the employer and co-workers (e.g., employment conditions, workload), the health care provider (e.g., supportive care needs, effective programs and interventions), and the community or society (e.g., economic and policy changes). The findings could contribute to the design of appropriate interventions and/or the provision of quality healthcare services and resources for ongoing surveillance of people living with, through and beyond cancer, and help determine what kinds of support survivors need. The study results could be used to better outline the management of a sequelae course of treatment for those who should undergo more intensive physical rehabilitation aimed at reducing the risk of adverse health outcomes, such as long-term health status burden, chronic comorbid conditions, and productivity-related disability levels.

Given the clinical significance of comorbidity in cancer survivors, this study may play a significant role in providing comprehensive evidence for health care

providers, including physical therapists and oncologists, who should be aware of the unique problems that challenge this population and who should advocate for prevention and evidence-based interventions.

This thesis has proposed new measurement levels of health status burden in terms of SF-36 scores. The levels of health status burden are proposed based on the magnitude of quality of life scores as follows: (1) high burden if the short form-36 (SF-36) scores < 50.00, (2) moderate burden if 50.00 ≤ SF-36 scores < 90.00, and (3) no burden if SF-36 scores ≥ 90.00. The levels of health status burden have captured the severity of disease for cancer patients. This proposed levels of health status burden will play a significant role in measuring the patient-level health burden.

Concerning the economic viewpoint, this study's (*Study 5*) findings are anticipated to support policy-makers in extending immunization programs by either switching to the *9-valent vaccine* or the inclusion of adolescent boys' vaccination, or extending the age of vaccination. This study is an extensive cost-effectiveness analysis of *9vHPV* vaccination in Australia from both the health system and societal perspectives. The introduction of *9vHPV* immunisation is assessed as being very cost-effective from both the health system and societal perspectives, by incorporating three delivery strategies (school-based, health facility-based, and outreach-based). Considering a two-dose schedule, the *9vHPV* vaccination demonstrated '*good value for money*', if the vaccination could accomplish a high vaccination coverage and provide protection. The findings of this evaluation contribute to decision-making about the incorporation of the *9vHPV* vaccine into a universal cervical cancer vaccination program in Australia. With continued assessment of the potential vaccine properties, as well as vaccine delivery and scale-up strategies, the two-dose *9vHPV* vaccine would provide significant health and economic benefits for preadolescents and society. Finally, the success of *9vHPV* vaccination will be contingent on several predominating factors including value for money, feasibility, acceptability, and affordability.

3.5 Future research directions

This study's findings have established a relationship between cancer burden and the long-term impacts on health status burden, chronic comorbid conditions, and productivity-related work disability among cancer survivors, which might vary in terms of cancer stages and types of cancer. However, the researcher was not able to estimate the cancer-specific health burden nor the work disability of cancer survivors due to the paucity of relevant data. A future study is required that will use a similar study design, perspective, and analytical methods in terms of cancer-specific exploration.

3.6 Conclusions

Resource scarcity is commonly recognised in healthcare provision worldwide, including Australia. This thesis has documented an understanding of the challenges of cancer outcomes and long-term consequences on health status burden, chronic comorbid conditions, and productivity-related work disability, and has provided an evaluation of cancer vaccination for preventing cancer-related infections, along with contributing to the ongoing debate of cancer research.

From the findings, it can be concluded that policies for cancer prevention strategies should have a high priority in policy discussions. If equally priced, the cancer vaccination option is the most economically viable intervention. Overall, this analysis has sought to contribute to an evidence-based recommendation about the new *9vHPV* vaccination in the national immunisation program in Australia. Apart from an economic standpoint, other factors should be considered for the national immunization program, such as budget availability, political issues, cultural influences and availability of a healthcare workforce. As cancer-related illness is life-threating for a high-risk population, the thesis argues that universal vaccination programs should be introduced as these early prevention programs could avert the number of cases, deaths, disability-adjusted life years, and hospitalisations. However, an optimum decision should be made by comparing vaccination programs

with alternative public health and healthcare low-cost interventions in Australia to reduce this burden (e.g., cancer case management strategies, other early cancer prevention programs, and increasing public health awareness about avoidable risks of cancer in the community). The findings have further implications for improving public health policy and reducing population-level unhealthy lifestyles, which should be recommended.

The overall burden of cancer is substantial in Australia across all socio-economic strata and geographical regions. Compared with socio-economically advantaged people, disadvantaged people had a substantially higher risk of cancer incidence and cancer-related mortality. Those living in remote areas also bear a higher burden than those in urban areas who are closer to prevention and treatment services. The findings of this study can inform efforts by health care policymakers and those involved in healthcare systems to improve cancer survival in Australia. This work further suggests that the provision of universal cancer care can reduce the burden by ensuring that curable and preventive cancer care services are accessible to all people regardless of socio-economic status or location. It is also significant for health care providers, including physical therapists and oncologists, who must manage the unique problems that challenge this population and who should advocate for prevention and evidence-based interventions by incorporating comprehensive social supports. In this context, more research on this public health problem is required before any decision should be made.

It is therefore anticipated that the present study will be useful for informing policymakers with the necessary knowledge to make rational investment choices in preventing cancer-related infections.

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Appendix A1

Appendix A1. Search strategies (study 5, article V)

PubMed

#1

(hpv[Title] OR papilloma*[Title] OR cervi*[Title]) AND (vaccine* OR vaccinated OR vaccination OR vaccinated OR immune*) AND (non-valent/ OR 9 or nine-valent/) AND (cost[Title/Abstract] OR costs[Title/ Abstract] OR cost-effective* OR cost-utility* OR cost-benefit*) AND (analysis OR economic evaluation*) AND (cervical cancer).

OR

#2 (((cost-effectiveness analysis OR cost-benefit analysis OR cost-utility analysis OR economic evaluation) AND (cervical cancer) AND (vaccine OR vaccination) AND (human papillomavirus OR HPV))) OR ((hpv[Title] OR papilloma* [Title] OR cervi*[Title]) AND (vaccine* OR vaccinated OR vaccination OR vaccinated OR immune*) AND (non-valent/ OR 9 or nine-valent/) AND (cost[Title/ Abstract] OR costs[Title/Abstract] OR cost-effective* OR cost-utility* OR cost-benefit*) AND (analysis OR economic evaluation*) AND cervical cancer)

Scopus

1

TITLE-ABS-KEY ("Economic evaluation" OR "Cost-effectiveness" OR "Cost-benefit analysis" OR "Cost-utility analysis" OR "Analysis" OR "Human papillomavirus" OR "HPV" OR "Vaccine" OR "Vaccinated" OR "Vaccination" OR "Cervical cancer" AND "non-valent" OR "9-Valent"))

2

TITLE-ABS-KEY("Economic evaluation" OR "Cost-effectiveness" OR "Cost-benefit analysis" OR "Cost-utility analysis" OR "Analysis" OR "Human papillomavirus" OR "HPV" OR "Vaccine" OR "Vaccinated" OR "Vaccination" OR "Cervical cancer" AND "non-valent" OR "9-Valent") AND (LIMIT-TO (PUBYEAR,2019) OR LIMIT-TO (PUBYEAR,2018) OR LIMIT-TO (PUBYEAR,2017) OR LIMIT-TO (PUBYEAR,2016) OR LIMIT-TO (PUBYEAR,2015) OR LIMIT-TO (PUBYEAR,2014) OR LIMIT-TO (PUBYEAR,2013) OR LIMIT-TO (PUBYEAR,2012) OR LIMIT-TO (PUBYEAR,2011) OR LIMIT-TO (PUBYEAR,2010) OR LIMIT-TO (PUBYEAR,2009) OR LIMIT-TO (PUBYEAR,2008) OR LIMIT-TO (PUBYEAR,2007) OR LIMIT-TO (PUBYEAR,2006) OR LIMIT-TO (PUBYEAR,2005) OR LIMIT-TO (PUBYEAR,2004) OR LIMIT-TO (PUBYEAR,2003) OR LIMIT-TO (PUBYEAR,2002) OR LIMIT-TO (PUBYEAR,2001) OR LIMIT-TO (PUBYEAR,2000))

Appendix A1

3

TITLE-ABS-KEY ("Economic evaluation" OR "Cost-effectiveness" OR "Cost-benefit analysis" OR "Cost-utility analysis" OR "Analysis" OR "Human papillomavirus" OR "HPV" OR "Vaccine" OR "Vaccinated" OR "Vaccination" OR "Cervical cancer" AND "non-valent" OR "9-Valent") AND (LIMIT

TO (PUBYEAR , 2019) OR LIMIT-TO (PUBYEAR , 2018) OR LIMIT-TO (PUBYEAR , 2017) OR LIMIT-TO (PUBYEAR , 2016) OR LIMIT-TO (PUBYEAR , 2015) OR LIMIT-TO (PUBYEAR , 2014) OR LIMIT-TO (PUBYEAR , 2013) OR LIMIT-TO (PUBYEAR , 2012) OR LIMIT-TO (PUBYEAR , 2011) OR LIMIT-TO (PUBYEAR , 2010) OR LIMIT-TO (PUBYEAR , 2009) OR LIMIT-TO (PUBYEAR , 2008) OR LIMIT-TO (PUBYEAR , 2007) OR LIMIT-TO (PUBYEAR , 2006) OR LIMIT-TO (PUBYEAR , 2005) OR LIMIT-TO (PUBYEAR , 2004) OR LIMIT-TO (PUBYEAR , 2003) OR LIMIT-TO (PUBYEAR , 2002) OR LIMIT-TO (PUBYEAR , 2001) OR LIMIT-TO (PUBYEAR , 2000)) AND (LIMIT-TO (DOCTYPE , "ar"))

PROSPERO
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Systematic review

This record cannot be edited because it has been rejected

1. * Review title.

Give the working title of the review, for example the one used for obtaining funding. Ideally the title should state succinctly the interventions or exposures being reviewed and the associated health or social problems. Where appropriate, the title should use the PI(E)COS structure to contain information on the Participants, Intervention (or Exposure) and Comparison groups, the Outcomes to be measured and Study designs to be included.

Mapping of the 9-Valent human papillomavirus (HPV) vaccination to prevent cervical cancer: A systematic review

2. Original language title.

For reviews in languages other than English, this field should be used to enter the title in the language of the review. This will be displayed together with the English language title.

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Review stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	No
Risk of bias (quality) assessment	Yes	No
Data analysis	No	No

Provide any other relevant information about the stage of the review here (e.g. Funded proposal, protocol not yet finalised).

6. * Named contact.

The named contact acts as the guarantor for the accuracy of the information presented in the register record.

Rashidul Mahumud

Email salutation (e.g. "Dr Smith" or "Joanne") for correspondence:

Mr Mahumud

7. * Named contact email.

Give the electronic mail address of the named contact.

rashidul.icddrb@gmail.com

8. Named contact address

Give the full postal address for the named contact.

Health Economics Research, Health Systems and Population Studies Division, icddr,b, 68, Shaheed

Tajuddin Ahmed Sarani, Mohakhali, Dhaka-1212, Bangladesh

9. Named contact phone number.

Give the telephone number for the named contact, including international dialling code.

8801913684183

10. * Organisational affiliation of the review.

Full title of the organisational affiliations for this review and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.

icddr,b

Organisation web address:

www.icddrb.org

11. * Review team members and their organisational affiliations.

Give the personal details and the organisational affiliations of each member of the review team. Affiliation refers to groups or organisations to which review team members belong. **NOTE: email and country are now mandatory fields for each person.**

Mr Rashidul Mahumud. icddr,b
Professor Khorshed Alam. Health Economics and Policy Research, University of Southern Queensland, QLD, Australia
Syed Karamat. Health Economics and Policy Research, University of Southern Queensland, QLD, Australia
Professor Jeff Gow. Health Economics and Policy Research, UNiversity of Southern Queensland, QLD, Australia
Professor Jeff Dunn. Cancer Council Queensland, Australia
Professor Khorshed Alam. Health Economics and Policy Research, University of Southern Queensland, QLD, Australia

12. * Funding sources/sponsors.

Give details of the individuals, organizations, groups or other legal entities who take responsibility for initiating, managing, sponsoring and/or financing the review. Include any unique identification numbers assigned to the review by the individuals or bodies listed.

The study was conducted during the first author's PhD research at the University of Southern Queensland,

Australia. This study was conducted without financial support from any institute or organization.

Grant number(s)

13. * Conflicts of interest.

List any conditions that could lead to actual or perceived undue influence on judgements concerning the main topic investigated in the review.

None

14. Collaborators.

Give the name and affiliation of any individuals or organisations who are working on the review but who are not listed as review team members. **NOTE: email and country are now mandatory fields for each person.**

Dr Shariful Islam. Deakin University

15. * Review question.

State the question(s) to be addressed by the review, clearly and precisely. Review questions may be specific or broad. It may be appropriate to break very broad questions down into a series of related more specific questions. Questions may be framed or refined using PI(E)COS where relevant.

What is the magnitude of cost-effectiveness of HPV vaccine to prevent cervical cancer?

16. * Searches.

State the sources that will be searched. Give the search dates, and any restrictions (e.g. language or publication period). Do NOT enter the full search strategy (it may be provided as a link or attachment.)

Scopus, PubMed, the Cochrane Library, Web of Science, Google Scholar, Academic Search, Global Health

and Embase databases will be searched systematically according to the eligibility criteria. The existing

literature in the cost-effectiveness of 9-valent HPV vaccination will be reviewed. Exclusion of articles will be

done based on: 'not cost-effectiveness analyses, 'insufficient cost and cost-effectiveness related data', or 'not using nine-valent HPV vaccine'. Language restrictions will not be considered.

17. URL to search strategy.

Give a link to a published pdf/word document detailing either the search strategy or an example of a search strategy for a specific database if available (including the keywords that will be used in the search strategies), or upload your search strategy.Do NOT provide links to your search results.

Alternatively, upload your search strategy to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

Yes I give permission for this file to be made publicly available

18. * Condition or domain being studied.

Give a short description of the disease, condition or healthcare domain being studied. This could include health and wellbeing outcomes.

Published original academic literature that had a quantitative nature to examine the cost-effectiveness of 9vHPV vaccination were included in the systematic review. This study was considered a wide type of study perspectives including societal and health systems

19. * Participants/population.

Give summary criteria for the participants or populations being studied by the review. The preferred format includes details of both inclusion and exclusion criteria.

Target population characteristics (e.g., gender-neutral, multiple age cohort immunization) will be considered in this review. Inclusion: adolescents and adults (less than 26 years old) will be considered the age group.

Exclusion: adults with more than 26 years old for male and female.

20. * Intervention(s), exposure(s).

Give full and clear descriptions or definitions of the nature of the interventions or the exposures to be reviewed.

To introduce HPV vaccine to prevent cervical cancer

21. * Comparator(s)/control.

Where relevant, give details of the alternatives against which the main subject/topic of the review will be compared (e.g. another intervention or a non-exposed control group). The preferred format includes details of both inclusion and exclusion criteria.

Vaccinated vs non-vaccinated

22. * Types of study to be included.

Give details of the types of study (study designs) eligible for inclusion in the review. If there are no restrictions on the types of study design eligible for inclusion, or certain study types are excluded, this should be stated. The preferred format includes details of both inclusion and exclusion criteria.

Published original academic literature that had a quantitative nature to examine the cost-effectiveness of 9-valent HPV vaccine were included in the systematic review

23. Context.

Give summary details of the setting and other relevant characteristics which help define the inclusion or exclusion criteria.

24. * Main outcome(s).

Give the pre-specified main (most important) outcomes of the review, including details of how the outcome is defined and measured and when these measurement are made, if these are part of the review inclusion criteria.

Incremental cost-effectiveness ratio (ICERs), DALY averted, QALY gained

* Measures of effect

Please specify the effect measure(s) for you main outcome(s) e.g. relative risks, odds ratios, risk difference, and/or 'number needed to treat.

To introduce nine-valent HPV vaccine to prevent cervical cancer

25. * Additional outcome(s).

List the pre-specified additional outcomes of the review, with a similar level of detail to that required for main outcomes. Where there are no additional outcomes please state 'None' or 'Not applicable' as appropriate to the review

None

* Measures of effect

Please specify the effect measure(s) for you additional outcome(s) e.g. relative risks, odds ratios, risk difference, and/or 'number needed to treat.

None

26. * Data extraction (selection and coding).

Describe how studies will be selected for inclusion. State what data will be extracted or obtained. State how this will be done and recorded.

The study selection process will be conducted in line with the PRISMA guidelines. Data extraction will be performed to develop a comprehensive data matrix which accurately summarises the study characteristics (e.g., authors, settings, perspective, threshold, outcome-related parameters and other necessary information), data needed for quality assessment.

Three authors of the review team independently examined the titles and abstracts identified by the search strategy and which meet the inclusion criteria. The remaining articles will be rechecked="checked" value="1" according to the inclusion criteria. The academic literature situated in the cost-effectiveness of 9-valent HPV vaccination will be reviewed. Exclusion of articles will be based on: 'not a cost-effectiveness analyses, 'insufficient cost and cost-effectiveness related data', or 'not using nine-valent HPV vaccine'. No language restrictions will not be applied.

27. * Risk of bias (quality) assessment.

Describe the method of assessing risk of bias or quality assessment. State which characteristics of the

studies will be assessed and any formal risk of bias tools that will be used.

Two authors independently assess the analytical quality of the preliminary selected studies using appropriate tools for examining risk of bias. Disagreements on a study inclusion will be resolved by discussion with a third review author. This study will follow the recommendations set out by research scholar to examine the likelihood of publication and data availability bias. It will describe the study-level and patient-level characteristics of the included studies. It will also report the systematic review from the selected papers that combines the aggregate data.

28. * Strategy for data synthesis.

Provide details of the planned synthesis including a rationale for the methods selected. This **must not be generic text** but should be **specific to your review** and describe how the proposed analysis will be applied to your data.

Two authors (RAM and SAK) independently will be reviewed the titles and abstract. Data from all eligible studies will be extracted by the same two authors using a standardized data collection form. A matrix will be developed to summarise the characteristics findings of the studies. Studies will be characterized by incorporating four themes: (i) study used 9-valent HPV vaccine to examine the cost-effectiveness, (ii) target population demographic characteristics (e.g., gender-neutral, multiple age cohort immunisation), (iii) study perspectives, model and economic level of each country, and (iii) model input and outcome-related parameters. To compare findings across selected studies, incremental cost-effectiveness ratios (ICERs) and standardized cost-effectiveness will be presented.

29. * Analysis of subgroups or subsets.

State any planned investigation of 'subgroups'. Be clear and specific about which type of study or participant will be included in each group or covariate investigated. State the planned analytic approach.

Settings and funding

Study questions and comparator

Analytical model

Thresholds and perspectives

Vaccine coverage

Vaccine efficacy

Number of vaccine dose and delivery route

Duration of vaccine protection, herd effect and discounting rate

Incremental cost-effectiveness ratio per DALY averted or QALY gained

30. * Type and method of review.

Select the type of review and the review method from the lists below. Select the health area(s) of interest for your review.

Type of review

Cost effectiveness

Yes

Diagnostic
No

Epidemiologic
No

Individual patient data (IPD) meta-analysis
No

Intervention
No

Meta-analysis
No

Methodology
No

Narrative synthesis
No

Network meta-analysis
No

Pre-clinical
No

Prevention
No

Prognostic
No

Prospective meta-analysis (PMA)
No

Review of reviews
No

Service delivery
No

Synthesis of qualitative studies
No

Systematic review
Yes

Other
No

Health area of the review

Alcohol/substance misuse/abuse
No

Blood and immune system
No

Cancer
Yes

Cardiovascular
No

Care of the elderly
No

Child health
No

Complementary therapies

No

COVID-19
No

Crime and justice
No

Dental
No

Digestive system
No

Ear, nose and throat
No

Education
No

Endocrine and metabolic disorders
No

Eye disorders
No

General interest
No

Genetics
No

Health inequalities/health equity
No

Infections and infestations
No

International development
No

Mental health and behavioural conditions
No

Musculoskeletal
No

Neurological
No

Nursing
No

Obstetrics and gynaecology
No

Oral health
No

Palliative care
No

Perioperative care
No

Physiotherapy
No

Pregnancy and childbirth
No

Public health (including social determinants of health)
No

Rehabilitation
No

Respiratory disorders
No

Service delivery
No

Skin disorders
No

Social care
No

Surgery
No

Tropical Medicine
No

Urological
No

Wounds, injuries and accidents
No

Violence and abuse
No

31. Language.

Select each language individually to add it to the list below, use the bin icon to remove any added in error.
English

There is an English language summary.

32. * Country.

Select the country in which the review is being carried out from the drop down list. For multi-national collaborations select all the countries involved.

Australia

33. Other registration details.

Give the name of any organisation where the systematic review title or protocol is registered (such as with The Campbell Collaboration, or The Joanna Briggs Institute) together with any unique identification number assigned. (N.B. Registration details for Cochrane protocols will be automatically entered). If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here. If none, leave blank.

34. Reference and/or URL for published protocol.

Give the citation and link for the published protocol, if there is one

Give the link to the published protocol.

Alternatively, upload your published protocol to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

Yes I give permission for this file to be made publicly available

Please note that the information required in the PROSPERO registration form must be completed in full even if access to a protocol is given.

35. Dissemination plans.

Give brief details of plans for communicating essential messages from the review to the appropriate

audiences.

Do you intend to publish the review on completion?

Yes

36. Keywords.

Give words or phrases that best describe the review. Separate keywords with a semicolon or new line. Keywords will help users find the review in the Register (the words do not appear in the public record but are included in searches). Be as specific and precise as possible. Avoid acronyms and abbreviations unless these are in wide use.

Cost-effectiveness analysis, 9 or nine-valent HPV vaccine, Cervical Cancer,

37. Details of any existing review of the same topic by the same authors.

Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible.

38. * Current review status.

Review status should be updated when the review is completed and when it is published. For newregistrations the review must be Ongoing.
Please provide anticipated publication date

Review_Ongoing

39. Any additional information.

Provide any other information the review team feel is relevant to the registration of the review.

40. Details of final report/publication(s) or preprints if available.

This field should be left empty until details of the completed review are available OR you have a link to a preprint.

Give the link to the published review.

Appendix A3. Systematic Review PRISMA Checklist (Study 5, Article V)

Appendix A3

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	*Mapping of cost-effectiveness evaluations of the 9-Valent human papillomavirus (HPV) vaccine: Evidence from a systematic review*	1
ABSTRACT			
Structured summary	2	**Introduction** The World Health Organization (WHO) recommends that programs for human papillomavirus (HPV) vaccination are established to be cost-effective before implementation. HPV vaccination is WHO recommended for girls aged 9–13 years old due to the high burden of cervical cancer. This review examined evidence of the cost-effectiveness evaluation of the 9-valent HPV vaccine within a global context. **Methods** Searches were performed until 31 July 2019 using two databases: PubMed and Scopus. A combined checklist (i.e., WHO, Drummond and CHEERS) was used to examine the quality of eligible studies. A total of 12 studies were eligible for review and nearly all were conducted in developed countries. **Results** Despite some heterogeneity in approaches to measuring cost-effectiveness, ten studies concluded that 9vHPV vaccination was cost-effective while two studies were not. The addition of adolescent boys into immunisation program was cost effective when vaccine price and coverage was comparatively low. When vaccination coverage for female was more than 75%, gender neutral HPV vaccination was less cost-effective than when targeting only girls aged 9–18 years. Multi cohort immunization approach was cost-effective in the age range of 9–14 years but the upper age limit at which vaccination was no longer cost-effective requires to be further evaluated. Most dominating parameters determined were duration of vaccine protection, time horizon, vaccine price, coverage, healthcare costs, efficacy and discounting rates. **Conclusions** These findings are anticipated to support policy-makers in extending HPV immunization programs on either switching to the 9-valent vaccine or inclusion of adolescent boys' vaccination or extending the age of vaccination. Further, this review also supports extending vaccination to low-resource settings where vaccine prices are competitive, donor funding is offered, cervical cancer burden is high and screening options are limited.	1
INTRODUCTION			
Rationale	3	Cervical cancer (CC) is both a leading cancer and the leading cause of cancer deaths in women globally [1]. Approximately 570,000 new cases of CC were diagnosed in 2018, composing 6.6% of all cancers in women [1]. The burden of CC is an alarming issue worldwide, especially in low- and middle-income countries (LMICs). Approximately 85% of CC cases and 90% of deaths from CC occur in LMICs [1]. Persistent infections with human papillomavirus (HPV) are a key cause of CC and is an established carcinogen of CC [2]. HPV is predominantly transmitted to reproductive-aged women through sexual contact [3]. Most HPV infections are transient and can be cleared up within a short duration, usually a few months after their acquisition. However, untreated HPV infections can continue and evolve into cancer in some cases. There are more than 100 types of HPV infections, and high-risk	2-3

		types develop into CC [4]. Thirteen high-risk HPV genotypes are known to be predominantly responsible for malignant and premalignant lesions of the anogenital area [5], and these are the leading causes of most aggressive CC [6]. Further, HPV is also responsible for the majority of anogenital cervical cancers, including anal cancers (88%), vulvar cancers (43%), invasive vaginal carcinomas (70%), and all penile cancers (50%) globally [4]. The burden of CC (i.e., high incidence and mortality rates) globally is preventable through the implementation of a primary prevention strategy such as vaccination [1]. There are vaccines that can protect common cancer-causing types of HPV and reduce the risk of CC significantly. Three types of HPV vaccines, namely bivalent (Cervarix), quadrivalent (Gardasil) and 9-valent vaccine (Gardasil-9), are currently available in the market. Unfortunately, as of March 2017, only 71 countries (37% of all countries) have introduced HPV vaccines in their national immunization programs for girls, and 11 countries (6%) for both sexes [2]. The first global recommendation on HPV vaccination was proposed by the World Health Organization's Strategic Advisory Group of Experts on Immunization in October 2008 [7], whereby HPV vaccination was recommended for girls aged 9–13 years old. This recommendation was updated in April 2014 [8], with the emphasis to include extended 2-dose HPV immunization for girls aged 9–14 years, who were not immunocompromised. With the recent licensing of the 9-valent vaccine and the introduction of various HPV vaccination strategies, an update on the current recommendations of HPV vaccination are inevitable. The goals of the immunisation program are to reduce the acquisition and spread of HPV infections and to achieve optimum coverage through effective delivery systems. According to the underlying distribution of HPV infection types of CC, the 9vHPV vaccine builds population-level strong immunity against HPV-6, 11, 16, 18, 31, 33, 45, 52, and 58 infections [5] that cumulatively contribute approximately 89% of all CCs globally [9]. Considering the primary prevention of HPV infection, the 9vHPV vaccine is expected to reduce by an additional 10% the lifetime risk of diagnosis with CC in immunised cohorts compared with the 4vHPV vaccine and reduce CC by an additional 52% in non-vaccinated cohorts [10].	
Objectives	4	This review aims to update current evidence on the economic viability of HPV vaccination. In addition, this study aims to examine the cost-effectiveness of the 9-valent vaccine when boys are included and when age cohorts are varied, all within a global context. This review may be used as comprehensive evidence of general trends on the ongoing cost-effectiveness evaluation of HPV vaccine.	3
METHODS			
Protocol and registration	5	The protocol has been submitted to PROSPERO, Centre for Reviews and Dissemination, University of York. https://www.crd.york.ac.uk/PROSPERO/#recordDetails. This protocol is under review that it is being assessed by the editorial team.	Under Review
Eligibility criteria	6	Three authors of the review team independently examined the titles and abstracts of the articles that met the selection criteria. The existing academic literature in the cost-effectiveness of 9-valent HPV vaccination was searched. Exclusion of articles was based on: 'not cost-effectiveness analyses, 'insufficient cost and cost-effectiveness related data', or 'not using nine-valent HPV vaccine'. Language restrictions were not applied.	4
Information sources	7	The literature search was performed by searching Scopus and PubMed to identify relevant articles following the inclusion criteria.	4

Search	8	Search inclusion terms included 'economic evaluation', 'cost-effectiveness', 'analysis', 'human papillomavirus', 'HPV', 'vaccine', 'vaccinated', 'vaccination', 'cervical cancer', 'non-valent', '9 or nine-valent'.	4
Study selection	9	Three authors of the review team independently examined the titles and abstracts of the articles that met the selection criteria (e.g., screening, eligibility), included in systematic review. The existing academic literature in the cost-effectiveness of 9-valent HPV vaccination was searched. Exclusion of articles was based on: 'not cost-effectiveness analyses, 'insufficient cost and cost-effectiveness related data', or 'not using nine-valent HPV vaccine'. Language restrictions were not applied. Four hundred and eighty one articles were yielded through the primary search, of which 78 articles were discarded because of duplication. Fifty one articles were considered for full-text review after screening by title and abstract. Of these, 12 articles were eligible for the final review. Three hundred fifty-two articles were excluded from this study following the inclusion criteria. The reasons for exclusion were: conference abstract (n = 58), reviews or editorials or commentary (n = 160), not cost-effectiveness evaluations (n = 60), did not use 9-valent vaccine (4v-HPV, 2v-HPV; n = 72) and insufficient information (n = 2). Finally, 12 articles were included in this review.	4-5
Data collection process	10	The study strategy followed a number of checks to ensure consistency of approach, including a discussion about discrepancies within the study team. For each outcome and model input parameters, the authors identified the proportion of missing observations and compare them with data in the original publication. In addition, a range of checks was carried out for all included studies to ensure that all values were reasonable. Datasets were combined to form a new master dataset where model input assumptions and outcome-related parameters used in the original studies were included. Further, two authors independently assessed the analytical quality of the preliminary selected studies using appropriate tools for examining risk of bias. Disagreements on inclusions were resolved by discussion with a third review author.	4
Data items	11	The study selection process was conducted in line with the PRISMA guidelines [11]. Data extraction was performed to develop a comprehensive data matrix which summarises the study characteristics such as authors, settings, perspective, threshold, outcome-related parameters and other necessary information. Two authors (RAM and SAK) independently reviewed the titles and abstract. Data from all eligible studies were extracted by the same two authors using a standardized data collection form. A matrix was developed to summarise the characteristics and findings of the studies. Studies were characterized by incorporating four themes: (i) study used 9-valent HPV vaccine to examine the cost-effectiveness, (ii) target population demographic characteristics (e.g., gender-neutral and multiple age cohort immunisation), (iii) study perspectives, model and economic level of each country, and (iv) model input and outcome-related parameters. The review showed evidence in terms of methodological and current practices of cost-effectiveness evaluation studies such as determination of study research questions; the study perspective adopted, the duration of vaccine protection, time horizon and discount rate; explanation of model performed for data analysis; model input assumptions behind the estimation of associated costs and outcome parameters; reporting of ICERs; most dominant parameters of sensitivity analysis; examination of study conclusions and recommendations as well as financial disclosure of the selected studies.	4-6
Risk of bias in individual studies	12	The study strategy followed a number of checks to ensure consistency of approach, including a discussion about discrepancies within the study team. For each outcome and model input parameters, the authors identified the proportion of missing observations and compare them with data in the original publication. In addition, a range of	4

		checks was carried out for all included studies to ensure that all values were reasonable. Datasets were combined to form a new master dataset where model input assumptions and outcome-related parameters used in the original studies were included. Further, two authors independently assessed the analytical quality of the preliminary selected studies using appropriate tools for examining risk of bias. Disagreements on inclusions were resolved by discussion with a third review author.	
Summary measures	13	Incremental cost-effectiveness ratio (ICERs), DALY averted, QALY gained, case averted, death averted	5
Synthesis of results	14	Two authors (RAM and SAK) independently reviewed the titles and abstract. Data from all eligible studies were extracted by the same two authors using a standardized data collection form. A matrix was developed to summarise the characteristics and findings of the studies. Studies were characterized by incorporating four themes: (i) study used 9-valent HPV vaccine to examine the cost-effectiveness, (ii) target population demographic characteristics (e.g., gender-neutral and multiple age cohort immunisation), (iii) study perspectives, model and economic level of each country, and (iv) model input and outcome-related parameters. To compare findings across the selected studies, incremental cost-effectiveness ratios (ICERs) and standardized cost-effectiveness were outlined. In terms of standardized cost-effectiveness scenarios, these studies used the heuristic cost-effectiveness threshold guided by the WHO [15], wherein an intervention or program was evaluated to be cost-effective if the ICER/DALYs averted was less than three times a country's annual per capita Gross Domestic Product (GDP). Further, the WHO constructed three broad decision rules: (i) an intervention or program was recommended as very cost-effective if ICER/DALYs averted <1 time GDP threshold; (ii) cost-effective if ICER/DALYs averted ≥ 1 time GDP threshold and ≤ 3 times GDP threshold; and (iii) not cost-effective if ICER/DALYs averted >3 times GDP threshold [16]. Examining whether an ICER offered by any strategy signifies value for money requires comparison to a cost-effectiveness threshold (CET). The CET refers to the health effects foregone (i.e., opportunity costs) related to resources being devoted to an intervention and consequentially being unavailable for other health-care priorities. Policy makers should be willing to invest their limited resources in the strategy offering the greatest health gains. CETs for the country with the lowest income in the world, borderline low/low-middle income, borderline low-middle/upper-middle income, and borderline high-middle/high income were estimated to be 1% to 51% GDP per capita, 4% to 51%, 11% to 51%, and 32% to 59%, respectively [17]. The review showed evidence in terms of methodological and current practices of cost-effectiveness evaluation studies such as determination of study research questions; the study perspective adopted, the duration of vaccine protection, time horizon and discount rate; explanation of model performed for data analysis; model input assumptions behind the estimation of associated costs and outcome parameters; reporting of ICERs; most dominant parameters of sensitivity analysis; examination of study conclusions and recommendations as well as financial disclosure of the selected studies.	5

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	The study strategy followed a number of checks to ensure consistency of approach, including a discussion about discrepancies within the study team. For each outcome and model input parameters, the authors identified the	

		proportion of missing observations and compare them with data in the original publication. In addition, a range of checks was carried out for all included studies to ensure that all values were reasonable. Datasets were combined to form a new master dataset where model input assumptions and outcome-related parameters used in the original studies were included. Further, three authors independently assessed the analytical quality of the preliminary selected studies using appropriate tools for examining risk of bias. Disagreements on inclusions were resolved by discussion with a third review author.	
Additional analyses	16	Not applicable	Not applicable
RESULTS			
Study selection	17	Four hundred and eighty one articles were yielded through the primary search, of which 78 articles were discarded because of duplication. Fifty one articles were considered for full-text review after screening by title and abstract. Of these, 12 articles were eligible for the final review. Three hundred fifty-two articles were excluded from this study following the inclusion criteria. The reasons for exclusion were: conference abstract (n = 58), reviews or editorials or commentary (n = 160), not cost-effectiveness evaluations (n = 60), did not use 9-valent vaccine (4v-HPV, 2v-HPV; n = 72) and insufficient information (n = 2). Finally, 12 articles were included in this review.	6
Study characteristics	18	Please see Table 1-3.	Please see Table 1-3
Risk of bias within studies	19	Not applicable	Not applicable
Results of individual studies	20	For all outcomes considered as economically viable of 9-valent vaccine across the countries.	8-9
Synthesis of results	21	Please see Table 3	Table 3
Risk of bias across studies	22	Not applicable	
Additional analysis	23	Not applicable	
DISCUSSION			
Summary of evidence	24	The HPV vaccination is one of the cornerstones of CC prevention worldwide. This study explored the cost-effectiveness of 9-valent HPV vaccination, drawing on 12 cost-effectiveness evaluations in order to inform and expand knowledge of the potential influence of the next generation of HPV vaccines. Most studies were conducted in developed countries while one study was performed in an LMIC. However, in the context of LMICs, the incidence of cervical cancer is an alarming public health concern, which warrants an increase in studies which can be extremely useful to influence local decision making [23]. The economic viability of gender-neutral 9-valent HPV vaccination was confirmed by three of the selected studies [13, 19, 20]. Cost-effectiveness exploration depends on the coverage of vaccination from the perspective of gender. For example, if the vaccine coverage for female recipients is 80% or above, the majority of the anogenital CC include vulvar cancers, invasive vaginal carcinomas cancers in female could	9-10

		be prevented. As a result, introduction of 9-valent vaccination for boys is relatively less important compared with girls due to the high economic costs involved without the additional benefits gained as per the female population reduction in CC, both from the societal and health system perspectives. Therefore, achieving optimal coverage of vaccination in females should remain a priority. This is of primary significance for LMICs settings since it is more effective and economically viable to prevent CC in females. However, it is also important to note that past studies paid little attention to the broader benefits of vaccination among male cohorts to prevent penile, anal, and oropharyngeal cancers. Exclusion of these diseases related to males may undermine the effectiveness of reducing CC. Gender-neutral vaccination might have several benefits including herd protection for boys. Moreover, it may provide indirect protection to unvaccinated women and direct protection to homosexual men. Therefore, this vaccination strategy should be further considerated in country-level immunization programs by underlining other parameters including disease burden, sexual behaviour in a country (e.g., homosexual intercourse), equity, budget impact, and affordability.	
Limitations	25	This review has some limitations. The cost-effectiveness evaluation based on GDP based thresholds of 1–3 times of GDP per capita lacks country specificity and has little meaning for country-level decision making [24]. It is uncertain whether this threshold truly reflects the country's affordability or societal willingness to pay for additional health gains. Additionally, GDP is originally intended to measure the experience of people residing in urban areas and thus, it may not actually reflect the experience of the entire population in a country, especially those living in rural areas. Apart from an economic standpoint, other factors should be considered for the national immunization program, such as budget availability, political issues, cultural influences and availability of healthcare workforce.	12
Conclusions	26	Current evidence does not show conclusive proof of greater cost-effectiveness of the new 9-valent vaccine. The inclusion of adolescent males in HPV vaccination programs is cost-effective if vaccine price or coverage of females is low and if the HPV-associated male diseases are also considered. Multiple age cohort vaccination strategy is likely to be cost-effective in the age range of 9–14 years, but the upper age limit at which HPV vaccination is no longer cost-effective needs to be further evaluated. Vaccine coverage, price, duration of protection and discount rates are important parameters for consideration in the uptake of HPV vaccination. Nonetheless, present study findings may be used as an evidence to policy-makers and healthcare providers in making recommendations for HPV national immunization programs on the new 9-valent vaccine or inclusion of adolescent boys' vaccination or extending the age of immunization, but it should not divert resources from vaccinating the primary target population of girls aged 12 years or from effective cervical cancer screening programs.	12
FUNDING			
Funding	27	This study was conducted without any financial supports.	

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

PRISMA 2009 Checklist

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Appendix A4. Media coverage of the PhD research findings

This PhD research finding has been shared in the **Australian Science Media Centre** as the following sub-title**:**

Sub-title of media articles:

Additional diseases can affect cancer burden in Aussie patients

Embargoed until: Publicly released: Thu 13 Feb 2020 at 0600 AEDT | 0800 NZDT2020-02-13 06:00

Around 63 percent of Aussie cancer patients suffer from at least one chronic disease, according to an observational study of over 2,000 cancer patients, and this can influence their cancer burden too. The researchers found the most prevalent comorbid conditions - relating to a medical condition that happens at the same time as another - were arthritis, osteoporosis, high blood pressure, hypertension, obesity, depression or anxiety, heart disease and asthma. Age, physical activity, nutrition, additional health issues and household income all contributed to how well patients were able to manage their diseases, and researchers say these risks should be taken into account during cancer treatment to help patients get through their treatment as smoothly as possible.

Link to website:
https://www.scimex.org/newsfeed/additional-diseases-can-affect-cancer-burden-in-aussiepatients?fbclid=IwAR0jbr2RxQ7BCT3KmwjFJzyVgxhvYTNMXBHTVQvyEf_mFFK10SfVTRihs-s

Journal/conference: PLOS One

DOI: 10.1371/journal.pone.0228744

Organisation/s: University of Southern Queensland, Cancer Council Queensland

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Original citation:
Mahumud, RA*, Alam, K, Dunn, J, Gow, J. The burden of chronic diseases among Australian cancer patients: Evidence from a longitudinal exploration, 2007-2017. PLoS ONE, 2020; 15(2): e0228744. https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0228744