School of Biomedical Sciences

Centre for Population Health Research

Evaluation of the trends and outcomes for women screened for and diagnosed with cervical precursor lesions: A Western Australian perspective

Aime Munro

This thesis is presented for the Degree of

Doctor of Philosophy

of

Curtin University

September 2015

Declaration

To the best of my knowledge and belief this thesis contains no material previously published by any other person except where due acknowledgement has been made.

This thesis contains no material that has been accepted for the award of any other degree or diploma in any other university.

The research presented and reported in this thesis was conducted in accordance with the National Health and Medical Research Council National Statement on Ethical Conduct in Human Research (2007) – updated March 2014.

The proposed research study received human research ethics approval from Curtin University Research Ethics Committee (EC00262), Approval Number HR 86/2012, and the Western Australian Department of Health Human Research Ethics Committee, Approval Number 2012/49.

Signature:

Date: 23 September 2015

Acknowledgements

Without the valuable expertise of several key individuals, the completion of thesis would not have been possible. I would like to express my sincere gratitude to all of you for your ongoing support and assistance over the last several years.

To my supervisors Professor James Semmens, Professor Peter O'Leary, Professor Jim Codde, and Associate Professor Vincent Williams: Your unwavering confidence in my ability to undertake this research has been motivating and I am truly grateful for the guidance that each one of you has consistently provided; most of all, I appreciate your patience and understanding that have helped me remain focused throughout this work.

Nerida Steel you have been a wonderful mentor and have taught me to question research findings ("so what" – what does this mean?) and truly showed me the value of population-based research. Without your trust and overall encouragement, this research would not have been possible. To the staff of the WA Cervical Cancer Prevention Program: Thank you for sharing your expertise and your devotion to serving Western Australian women is nothing short of admirable.

To the clinicians at King Edward Memorial Hospital - Professor Yee Leung, Dr Paul Cohen, and Dr Colin Stewart: Your approach to women's health, research, and innovative thinking has been inspiring. Through your guidance, mentorship and support, I have truly come to appreciate the meaning of "translating research" into clinical practice.

To all the staff members within the Centre for Population Health Research at Curtin University: A huge and sincere thank you is extended to all. Dr Katrina Spilsbury you have been my "rock", coffee companion, and voice of reason throughout this entire process. Peter Bloor, you have never failed to ensure I felt like a true team member! Rene Forsyth, you have kept me strong throughout our biostatistics course work and have become a truly valued friend.

To my family, Mum, Dad, Alexander, and Sally: Thank you for your unconditional support and giving me the freedom to pursue my passions. Finally, to Rhys: I cannot thank you enough for being a generous and understanding partner; I can't wait to embark on our next adventure together with Noah.

Research output from this thesis

Published manuscripts

1. **Munro A,** Williams V, Semmens J, Leung Y, Stewart CJR, Codde J, Spilsbury K, Steel N, Cohen P, O'Leary P. **Risk of high-grade cervical dysplasia and gynaecological malignancies following the cytologic diagnosis of atypical endocervical cells of undetermined significance: A retrospective study of a state-wide screening population in Western Australia.** *A N Z J Obstet Gyn* 2015; 55(3): 268-73.

2. **Munro A,** Leung Y, Spilsbury K, Semmens J, Codde J, O'Leary P, Williams V, Steel N, Cohen P. **Comparison of cold knife cone biopsy and loop electrosurgical excision procedure in the management of cervical adenocarcinoma in situ: What is the gold standard?** *Gynecol Oncol* 2015; 137(2): 258-63.

3. **Munro A,** Powell R, Cohen P, Bowen S, Spilsbury K, Codde J, Semmens J, O'Leary P, Williams V, Leung Y. **Spontaneous regression of CIN2 in women aged 18-24 years: a retrospective study of a state-wide population in Western Australia.** *Accepted for publication 21 November 2015 by Acta Obstetricia et Gynecologica Scandinavica* (manuscript ID: AOGS-15-0599.R1).

4. **Munro A,** Codde J, Semmens J, Spilsbury K, Williams V, Steel N, Cohen P, Pavicic H, Westoby V, O'Leary P. **Utilisation of co-testing (human papillomavirus DNA testing and cervical cytology) after treatment of CIN: A survey of GP's awareness and knowledge.** *AFP* 2015; 44(1): 64-8.

5. **Munro A,** Spilsbury K, Leung Y, O'Leary P, Williams V, Codde J, Steel N, Cohen P, Semmens J. **The Human Papillomavirus 'Test of Cure': A lesson on compliance with the NHMRC Guidelines on Screening to Prevent Cervical Cancer.** *A N Z J Obstet Gyn* 2015; 55(2): 185-90.

6. **Munro A**, Pavicic H, Leung Y, Westoby V, Steel N, Semmens J, O'Leary P. **The role of general practitioners in the continued success of the National Cervical Screening Program.** *AFP* 2014; 43(5): 293-296.

Conference presentations

1. Powell R, **Munro A,** Bowen S, O'Leary P, Semmens JB, Codde J, Williams V, Spilsbury K, Steel N, Leung Y. **CIN2 regression for young patients who were conservatively managed.** *15th Biennial Meeting of the International Gynecologic Cancer Society,* Melbourne, Australia. November 2014.

2. Powell R, **Munro A,** Bowen S, O'Leary P, Semmens JB, Codde J, Williams V, Spilsbury K, Steel N, Leung Y. **CIN2 regression for young patients who were conservatively managed.** *2014 World Cancer Congress,* Melbourne Australia. December 2014.

3. **Munro A,** Williams V, Semmens JB, Leung Y, Stewart CJR, Codde J, Spilsbury K, Steel N, O'Leary P. **High-grade abnormality following the cytologic diagnosis of atypical endocervical cells of undetermined significance: A retrospective study of 1736 cases.** *15th Biennial Meeting of the International Gynecologic Cancer Society,* Melbourne Australia. November 2014.

4. **Munro A,** Codde J, Semmens J, Spilsbury K, Williams V, Steel N, Cohen P, Pavicic H, Westoby V, O'Leary P. **Utilisation of cotesting (human papillomavirus DNA and cervical cytology) after treatment of CIN: A survey of GPs awareness and knowledge.** *2014 World Cancer Congress,* Melbourne, Australia. December 2015.

5. **Munro A,** Leung Y, Spilsbury K, Semmens J, Codde J, O'Leary P, Williams V, Steel N, Cohen P. **CKC or LEEP for ACIS? What is the Gold Standard?** *2015 Australian Society of Gynaecologic Oncologists Scientific Meeting*, Penang, Malaysia. July 2015.

Other translation output

1. **Munro A,** Pavicic H, Leung Y, Westoby V, Steel N, Semmens J, O'Leary P **Preventing cervical cancer: Encouraging women's participation in cervical screening**. Perth: WA Cervical Cancer Prevention Program; 2013.

2. **Munro A,** Pavicic H, Steel N. **Cervical screening: synopsis for WA Pap smear providers**. Perth: WA Cervical Cancer Prevention Program; 2013.

3. Steel N, **Munro A**, Pavicic H, Fletcher C, O'Leary P, Williams V, Codde J, Semmens J. **Clinical information for health professionals.** Perth: WA Cervical Cancer Prevention Program; 2013.

Award nomination

The candidate was nominated for the *2014 Rising Stars Award* by the Women and Infants' Research Foundation. This nomination celebrates and showcases WA's top emerging medical researchers.
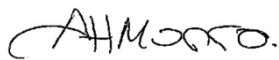
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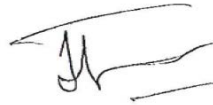
Statement of contribution

This thesis originated from my employment at the WA Cervical Cancer Prevention Program (WA Health), and subsequent research ideas were further developed in collaboration with my supervisors and other co-authors.

I have led the development of this thesis from 2012 including the obtainment of ethical approval, concept development management of data collection, data validation, data analysis, and dissemination of research findings (development of manuscripts, posters, and verbal presentations). All co-authors have endorsed and acknowledged my level of contribution. *The Statement of Contribution of Others* for each publication is presented in Appendix 1.

Signed:

Aime Munro
Candidate

Professor James B. Semmens
Supervisor

Date: 23 September 2015

Table of Contents

List of Tables

Table of Figures

Abbreviations

AEC	Atypical endocervical cells
ACIS	Adenocarcinoma in situ
AMBS	Australian Modified Bethesda System (2004)
CIN1-3	Cellular intraepithelial neoplasia grade 1-3
CKC	Cold knife cone biopsy
CSR	Cervical Screening Register
DNA	Deoxyribonucleic acid
GP	General Practitioner
HMDC	Hospital morbidity data collection
HPV	Human papillomavirus
HR HPV	High-risk HPV type
HSIL	High-grade squamous intraepithelial lesion
IARC	International Agency for Research on Cancer
LEEP	Loop electrosurgical excision procedure
LLETZ	Large loop excision of the transformation zone
LSIL	Low-grade squamous intraepithelial lesion
NCSP	National Cervical Screening Program
NHMRC	National Health and Medical Research Council
ToC	Test of Cure
WA	Western Australia
WACCPP	WA Cervical Cancer Prevention Program
WADLS	Western Australian Data Linkage System

Exegesis

Explanatory overview

The World Health Organization reports that cervical cancer is the second most common malignancy that affects women worldwide[1]. Cervical cancer is defined by the National Cancer Institute as a malignancy that is formed in the tissue of the cervix, which is typically, asymptomatic and slow growing in nature. In 2011 alone, 682 Australian women were diagnosed with cervical cancer, with the majority of the women aged between 30 and 59 years[2]. In 2012, there were 143 deaths from cervical cancer among women aged 20–69 years, the target population of the Australian National Cervical Screening Program (NCSP), equating to 1.9 deaths per 100,000 women (age-standardised)[2]. There were 226 deaths or 1.8 deaths per 100,000 women (age-standardised) among women of all ages[2].

Cervical cancer is highly preventable through cytologic screening programs that facilitate the detection and treatment of precancerous lesions[2, 3]. Consequently in 1991, the Australian Health Ministers' Advisory Council implemented Australia's cervical screening program, now known as the NCSP. The NCSP operates as a joint program of the Australian Government and state and territory governments, targeting women aged 20–69. Since the NCSP was introduced in Australia, Pap smear testing has been associated with a sustained 50% reduction in cervical cancer incidence (7 new cases per 100,000 women of all ages compared to the previous figure of 18 new cases per year prior to the introduction of the NCSP) and mortality (4.0 to 1.8 deaths per 100,000 for women of all ages)[2].

When cervical cancer does occur, it most commonly presents amongst women who have never been screened or who have not been screened within the previous 5 years[2, 3, 5, 6] suggesting that women's successful adherence to population-based cervical screening recommendations will assist in further reducing the morbidity and mortality linked to cervical cancer[2, 3, 5, 6].

Early detection greatly improves the chances of successful treatment and prevents early cervical changes from becoming malignant, however appropriate management of women with biopsy confirmed cervical pre-cancer is also a critical component of cervical cancer prevention programs[3, 7]. In Australia, the National Health and Medical Research Council (NHMRC) developed recommendations for practitioners to manage women with abnormal cervical screening test results and cervical cancer precursor lesions published in the *"Screening to present cervical cancer: Guidelines for the management of asymptomatic women with screen-detected abnormalities"* and referred to as The Guidelines[3].

The most recent revised recommendations were implemented in July 2005 and replaced the initial 1994 guidelines[3]. These revised guidelines addressed the state of cervical cancer in Australia and were based on clarification of the biology and behaviour of cervical squamous disease and improved understanding of the diagnosis of endocervical glandular disease. The 2005 Guidelines included the treatment of glandular abnormalities that were emerging as an additional management problem due to improved recognition of precancerous changes in screening smears (e.g. the overall number of endocervical abnormalities increased from 914 in 2006 to 1,172 in 2013, with 67.2% biopsy samples confirmed as adenocarcinoma in situ (ACIS)[2]) and conservative treatment options for young women and the effectiveness of follow-up for women treated for high-grade squamous intraepithelial lesions (HSIL)[3].

As the 10th anniversary since the introduction of the guidelines approaches, it is timely to undertake a review of the efficacy of its management recommendations based on an analysis of screening and treatment data for squamous and glandular lesions held by the Cervical Screening Registry of WA. Among the myriad outcome scenarios that will be addressed in this investigation are i) the clinical significance of low-grade glandular abnormalities, ii) the effectiveness of conservative treatment modalities in young women diagnosed with CIN2 or AIS, and iii) practitioners' compliance with follow-up recommendations for all women treated for CIN2/3. Drawing on more recent available evidence will support a revision of Australian management guidelines (due to be completed by 2017).

The work in this thesis largely draws on unique linked data system (Cervical Screening Registry of Western Australia (WA), Hospital Morbidity Database System, WA Cancer Registry and WA Death Registrations) available in WA; this research is well placed to inform the above-mentioned process by adding to the evidence pool for the revision of The Guidelines.

Thesis objectives

The Guidelines for the management of Australian women with abnormal cervical test results will be revised by 2017. Consequently, the purpose of this research was to conduct epidemiologic population-based studies on the following critical topics that require evidence-based management recommendations to be developed.

As this thesis is by publication, each chapter title page presents an overview of research output achieved and relevant publication(s) is presented at the end of each section. No publication is presented more than once within the manuscript. Additional output that resulted from this thesis, including delivery of presentations (i.e. UWA Rising Star's Event and "What is the Gold Standard") is presented in the appendices and translational material is located in the additional material section.

Objective 1

Investigate the risk factors and incidence of atypical endocervical cells of undetermined significance for Western Australian women in Pap smear test results and the associated health outcomes.

Objective 2

Analyse linked population-based administrative data to evaluate women with histologically confirmed adenocarcinoma in situ managed with conservative treatment in Western Australia.

Objective 3

Utilise linked population-based administrative data to investigate the spontaneous clearance rate among young women (aged <25 years) with histologically confirmed cervical intraepithelial lesion (grade 2).

Objective 4

Determine practitioners' knowledge, awareness, and compliance with the Test of Cure management pathway.

Thesis overview

This thesis presents a summary of the work undertaken to address the thesis objectives. It is divided into five chapters and is supported by six published publications in peer-reviewed journals (the candidate was first author on all publications). A further manuscript was accepted 21 November 2015 by *Acta Obstetricia et Gynecologica Scandinavica* (manuscript ID: AOGS-15-0599.R1).

Chapter 1:   Literature review: Classification, treatment and follow-up o cervical epithelial lesions and data integration.

Presents a literature review and addresses Objective 1 by describing the development and treatment of cervical cancer precursor lesions. A description of the "big data revolution", administrative data and the role of the Western Australian Data Linkage System are also presented. Objective 1 resulted in one publication.

Chapter 2:   Investigation of the clinical significance of cytologically detected endocervical (glandular) abnormalities.

Addressed Objective 2 by exploring women's health outcomes after being diagnosed with a low-grade glandular lesion and resulted in one publication.

Chapter 3:   Investigation of the effectiveness of conservative treatment for high-grade endocervical (glandular) abnormalities.

Explores the efficacy of conservative treatment for women diagnosed with adenocarcinoma in situ and addressed Objective 3 (resulting in 1 publication). Chapter three also outlines the Western Australian Data Linkage System and how administrative data are used to support this research.

Chapter 4:   Spontaneous regression of CIN2: Investigation of incidence in women aged 18 to 24 years.

Addressed Objective 4 by investigating the spontaneous regression of CIN2 in young women and their associated health outcomes. Chapter four resulted in one publication that was accepted 21 November 2015 by *Acta Obstetricia et Gynecologica Scandinavica* (manuscript ID: AOGS-15-0599.R1).

Chapter 5:   Investigation into the follow-up of women treated for high-grade intraepithelial lesions

Addressed Objective 5 by exploring GP awareness/knowledge and compliance with the Test of Cure management pathway. Chapter 5 resulted in two publications.

Chapter 6:   Discussion

Presents the final discussion and explores the overall strengths and limitations of the work reported in this thesis. Additionally, areas for future research to be undertaken are discussed within Chapter 6.

Chapter 1:

Literature review: Classification, treatment and follow-up of cervical epithelial lesions, administrative data and data integration

<u>**Research output**</u>

Published manuscripts

1. **Munro A**, Pavicic H, Leung Y, Westoby V, Steel N, Semmens J, O'Leary P. **The role of general practitioners in the continued success of the National Cervical Screening Program.** *AFP* 2014; 43(5): 293-296.
2. Pavicic H., **Munro A**, Steel N. **Cervical cancer prevention toolkit for Australian nurses and midwives.** *ANJ* 2013; 21(2): 30-33.

Other translational output

1. **Munro A,** Pavicic H, Leung Y, Westoby V, Steel N, Semmens J, O'Leary P **Preventing cervical cancer: Encouraging women's participation in cervical screening.** Perth: WA Cervical Cancer Prevention Program; 2013.
2. Munro A, Pavicic H, Steel N. **Cervical screening: synopsis for WA Pap smear providers.** Perth: WA Cervical Cancer Prevention Program; 2013.
3. Steel N, Munro A, Pavicic H, Fletcher C, O'Leary P, Williams V, Codde J, Semmens J. **Clinical information for health professionals.** Perth: WA Cervical Cancer Prevention Program; 2013.

1.1 Introduction

This chapter formed the basis for a literature review, which was published by the Australian Family Physician. Additionally, content from this section was used to develop the content of WA Cervical Cancer Prevention Program's website for health care providers (Additional Material 1), a Cervical Cancer Prevention Toolkit for Australian Midwives and Nurses (Additional Material 2) and the Western Australian Pap Smear Provider Synopsis (Additional Material 3).

In many developing countries, cervical cancer remains the most common cancer among women and is recognised as a leading cause of death[1]. Fortunately, cervical cancer is a highly preventable disease if precancerous lesions are detected and treated in a timely manner[1-5, 7-9]. With our increased knowledge of the pathogenesis of cervical cancer and advancements in techniques of clinical diagnosis, new and interesting options for the prevention of cervical cancer have emerged[1]. Different methods for the prevention of cervical cancer are now available, namely cervical cytology screening (i.e. conventional cytology (Pap smear) or liquid-based cytology), human papillomavirus (HPV) screening, and vaccination against HPV[1].

In 1991, the Australian Government implemented the National Cervical Screening Program (NCSP), which is an organised population-based program that utilises the Pap smear as a screening tool to detect abnormal cervical changes and implement the necessary interventions for prevention of progression to cancer[2, 4]. In 2013 alone, after age-standardisation (the 2001 Australian Standard Population), for every 1,000 Australian women (aged 20 to 69 years) screened, 8.5 had biopsy-confirmed high-grade cervical abnormality (high-grade squamous intraepithelial lesion (HSIL) or adenocarcinoma in situ (ACIS))[2]. The detection of these high-grade abnormalities provides an opportunity for curative treatment avoiding potential progression to invasive cancer[2].

In 2007, Australia became the first country to adopt a National HPV Vaccination Program (NHVP)[10], delivered through a school-based approach, providing HPV vaccination to girls and boys aged between 12 and 13 years. Preliminary analyses on the effectiveness of the NHVP (within five years of the program's implementation) indicate a substantial reduction in low- and high-grade cervical abnormalities in women who received the HPV vaccine dose through the school-based program[10].

The Australian recommendations for the management of patients with abnormal cervical test results (cervical cytology and/or biopsy) are outlined by the National

Health and Medical Research Council (NHMRC) in *Screening to prevent cervical cancer: Guidelines for the management of asymptomatic women with screen detected abnormalities*[7]. Compliance with clinical practice and management guidelines by health care providers has been shown to reduce the morbidity and mortality attributable to cervical cancer[1-4, 9]. In 2014, the Australian Department of Health determined that the 2005 NHMRC Guidelines needed to undergo review and be updated to support the implementation of a revised cervical screening pathway scheduled to be adopted in Australia by 2017[2].

1.2 Anatomy of the cervix

The uterine cervix is the lower part of the uterus. The cervix consists of three main parts (Figure 1)[11]:

- The ectocervix (portio vaginalis) is the part of the cervix that projects into the vagina and is visualised using a speculum in a gynaecologic examination. This region, like the vagina is covered with stratified squamous epithelium.
- The endocervix comprises highly branched glands and is lined by secretory columnar epithelium and forms the endocervical canal, which is continuous with the endometrial canal. The endocervix is not seen in a speculum examination, and commences in the region of the external os.
- The abrupt boundary of the ectocervix and endocervix occurs where the lining cells change from squamous to glandular type and is called the squamo-columnar junction (SCJ). The location of the SCJ will vary according to age, hormonal status and parity[12].

Although all cervical cancers share the same site code (C53 under the International Classification of Diseases 10), there are a number of histological subtypes within the cervical cancer category. The most prevalent types (91.2% of all cervical cancer cases in Australia) of cervical cancer can be split into two main categories I) squamous cell carcinoma (which arises from the squamous cells that cover the outer surface of the cervix); and II) adenocarcinoma (which arises from the glandular (columnar) cells in the endocervical canal). In 2011, 457 new cases of squamous cell carcinomas were confirmed and 165 women were diagnosed with adenocarcinoma[2].

Figure 1. Anatomy of the cervix presenting the ectocervix, endocervix, external os, and the transformation zone[12]
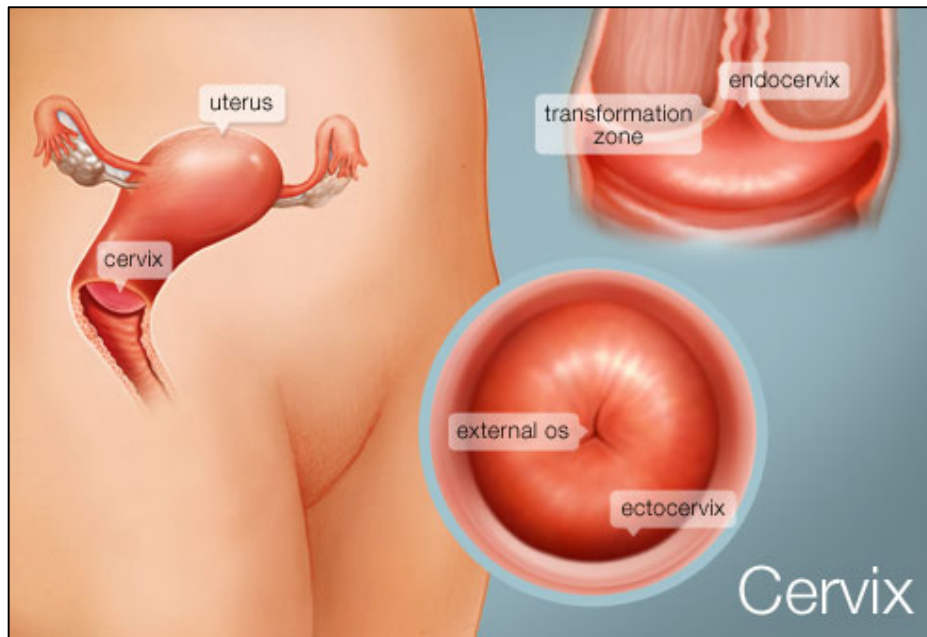
1.3 Pathogenesis and natural history of cervical cancer and precursor lesions

Improved understanding of the biology of cervical carcinoma has revealed that the main causative factor is persistent infection with oncogenic high-risk human papillomavirus (HR HPV), specifically types 16 and 18[14, 17, 18, 20-23]. There are 16 HR HPV types that have been linked to anogenital carcinoma in humans, of which 12 (16,18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59) have been definitively classified as oncogenic[24, 25]. Epidemiological evidence has highlighted other contributing risk factors that may influence the development of cervical cancer and its precursors, including tobacco smoking, long-term oral contraceptive pill use, human immunodeficiency virus infection, high parity, *Herpes simplex* virus infection, *Chlamydia trachomatis* infection as well as immune system suppression[13-19].

The International Agency for Research on Cancer coordinated a multicentre case-control study which concluded that persistent HR HPV infection is a critical for the development of cervical cancer (squamous cell carcinoma and adenocarcinoma)[8, 19]. That study showed HR HPV DNA was present in 99.7% of 1,000 cervical cancer histological specimens collected from 22 countries worldwide[19, 26]. Furthermore, several cohort studies have since confirmed that persistent oncogenic HPV infection and high risk of developing cervical cancer were strongly related[23, 27, 28].

Typically anogenital HPV infection occurs through sexual contact[17, 24, 29]. The risk factors for HR HPV infection are related to the individual's sexual behaviour i.e. age at sexual debut and lifetime number of sexual partners [9-15]. The incidence of HPV infection varies in different regions of the world; however, it is found to peak in 20–30% of young women aged 20–24 years with a clear decline (3–10%) among women aged over 30 years[19, 27, 28]. It is estimated that more than 90% of young women (aged less than 30 years) infected with HPV will naturally clear the virus within 12–18 months of first acquisition[29]. Only a small proportion of women who are chronic carriers of HR HPVs are at increased risk of progression and development of neoplastic lesions of the anogenital tract[23].

1.4 Classification of cervical abnormalities

In 2001, the National Advisory Committee to the National Cervical Screening Program (NCSP)[7] requested that the management guidelines publication entitled *Screening to Prevent Cervical Cancer: Guidelines for the Management of Women with Screen Detected Abnormalities* be revised. This request was made to ensure that The Guidelines accurately reflected the contemporary understanding of the relationship between HPV, cervical cancer and its precursors[7]. Consequently, the NCSP established an Australian working party of experts to consider the adoption of the International classification for the diagnosis and management of cervical disease known as the Bethesda System[7]. The working party developed a unique terminology system suited for Australian code of practice known as the Australian Modified Bethesda System 2004 (AMBS)[7]. That was subsequently adopted. The AMBS is used to classify cervical cellular changes (squamous and glandular) in Pap smears and to outline standard follow-up recommendations[7].

Classification of the more prevalent squamous intraepithelial lesions (Table 1) is based on the features of morphologic changes in cells in Pap smears and biopsy specimens that reflected abnormal cellular proliferation and maturation, together with nuclear atypia. In low-grade intraepithelial squamous lesions (LSILs), the observed cellular changes occupy the upper third of the epithelium and may include the cytopathic effect (koilocytosis) of HPV. In the case of HSILs, the abnormal changes occur in the lower two thirds or entire thickness of the epithelium and HSILs demonstrate the presence of HR HPV as well as chromosomal instability[30].

The AMBS also recognises four categories for classifying glandular abnormalities (Table 2)[7]. ACIS is much less commonly diagnosed than squamous preinvasive lesions[32]. In Australia, the overall number of biopsy-confirmed endocervical

(glandular) abnormalities increased from 868 in 2005 to 1,172 in 2013[2]. In 2013, 67.2% of all glandular abnormalities were high-grade including endocervical dysplasia and ACIS[2]. No terminology for glandular lesions with lower degrees of nuclear atypia has been recognised owing to the rarity of biopsy samples[31-33].

1.5 Treatment of cervical epithelial abnormalities in Australia

The National Health Medical Research Council (NHMRC) Guidelines for *The Management of Asymptomatic Women with Screen Detected Abnormalities* were implemented in 2005 as a guide for the treatment and follow-up of patients with squamous and glandular abnormalities (Table 1 and Table 2) to reduce cervical cancer incidence and mortality rates in Australia. To ensure clinical consensus these management guidelines were developed through national consultation with the relevant professional bodies, clinicians and consumers[7].

In Australia, best practice considers histological biopsy confirmation of cervical disease necessary prior to delivering treatment[7]. The adherence to management guidelines and appropriate clinical follow-up of women with high-grade cervical lesions has been a critical component of the success of the Australian National Cervical Screening Program (NCSP)[2, 4, 7].

1.5.1 Low-grade cervical epithelial abnormalities

1.5.1.1 Squamous cells (see Table 1 (A and B))

In Australia, in cases where a low-grade squamous cervical abnormality is detected by cervical cytology, conservative management is recommended typically as repeat Pap smear within 12 months[7]. An exception to this recommendation is made for women aged over 30 years who have not had a negative screening history for the prior three-year period[7]. These women are directed straight to colposcopy for immediate investigation. Australian management guidelines also recommend that women aged over 30 years be offered immediate colposcopy and/or undergo a further Pap smear within six months of initial low-grade abnormality to ensure timely detection of potential occult HSIL[7].

Table 1. The Australian Modified Bethesda System (AMBS 2004) for squamous abnormalities[7]
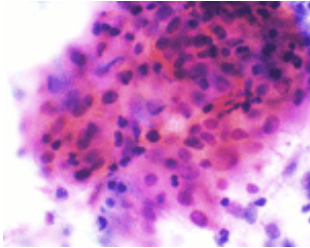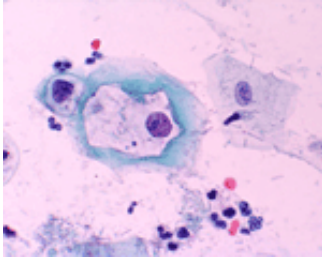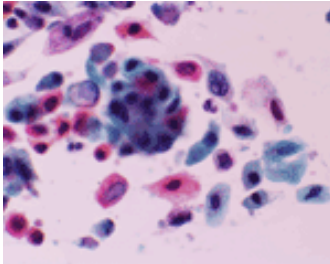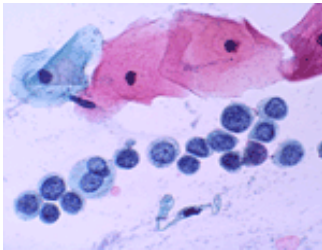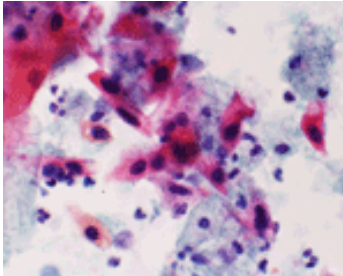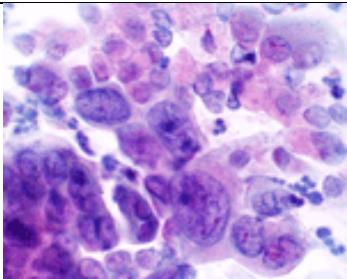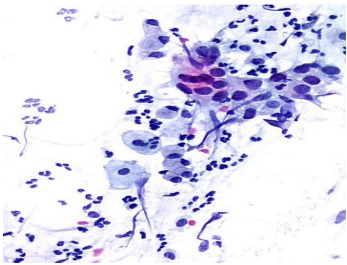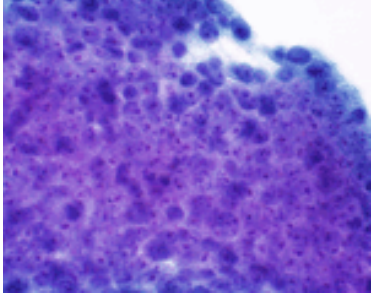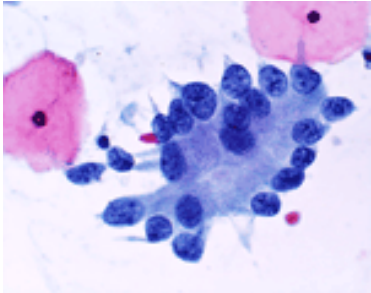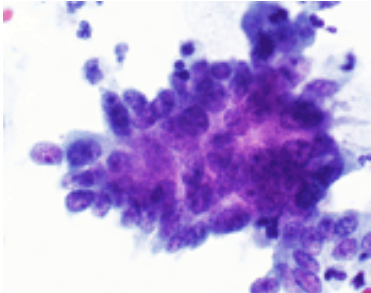
	AMBS 2004	Features	Cervical Cytology Image[34]
A	Possible low-grade squamous intraepithelial lesion	Nonspecific minor squamous cell changes. Changes that suggest but fall short of HPV/CIN 1	
B	Low-grade squamous intraepithelial lesion	HPV effect, CIN 1	
C	Possible high-grade squamous lesion	Changes that suggest, but fall short of, CIN 2, CIN 3, or SCC	
D	High-grade squamous intraepithelial lesion	CIN 2, CIN 3	
E	Squamous cell carcinoma	Squamous cell carcinoma	

Table 2. The Australian Modified Bethesda System (AMBS 2004) for glandular abnormalities[7]

	AMBS 2004	Features	Cervical Cytology Image[34]
F	Atypical endocervical cells of undetermined significance	Nonspecific minor cell changes in endocervical cells	
G	Atypical glandular cells of undetermined significance	Nonspecific minor cell changes in glandular cells	
H	Possible high-grade glandular lesion	Changes that suggest, but fall short of, AIS or adenocarcinoma	
I	Endocervical adenocarcinoma in situ	Adenocarcinoma in situ	
J	Adenocarcinoma	Adenocarcinoma	

In Australia, positive results for low-grade squamous abnormalities are commonly reported (4.5%) cytology. This can partly be a consequence of the young age at which cervical screening commences (18 to 20 years of age) as well the two-yearly rescreening interval that detects transient abnormalities[7, 35]. Given the prevalence of possible LSILs and LSILs, the optimal management of these women with these test results positive cervical test results is clear, although internationally countries are now recommending patients adhere to follow-up procedures such a cytological surveillance, HPV testing and/or colposcopy[3, 7, 36].

1.5.1.2 Glandular cells (Table 2 (F))

The current management practices for possible LSIL and LSIL is supported by current evidence, however, the management of women with a low-grade glandular lesion remains unclear due to the rarity of this lesion (Publication I). Cytology test results that report a possible low-grade or low-grade glandular lesion were very rare and accounted for only 0.04% of Australian cytology test results in 2012[2]. Several studies have demonstrated that AEC may be associated with premalignant or malignant cervical lesions but most have been limited by short follow-up periods and/or relatively small numbers of cases[39-42]. Furthermore, the risk of significant pathology has not always been correlated with age, prior smear history, presence of endocervical cells in preceding cytology samples and/or the socio-economic status of the patient. Consequently, in Australia, women with a suspected low-grade glandular lesion should be directly referred to colposcopic assessment to determine if a more severe lesion is present[7]. The clinical significance of this lesion and associated health outcomes for affected women have been reported in Publication I and further assists practitioners in the management of these patients.

1.5.2 High-grade squamous intraepithelial lesions

Women with high-grade abnormality on cytology test results are recommended to undergo colposcopic examination to assess the transformation zone for the severity of the lesion and to improve the accuracy of a targeted biopsy[7]. Cervical lesions that are biopsy confirmed as CIN 2 or CIN 3 (Table 1 (D)) are treated using the same approach, as the distinction between the two grades is often ambiguous[7, 46]. Given that CIN 2/3 have a high risk of disease progression, prompt treatment, within two months of diagnosis, is recommended in Australia[7]. CIN2/3 may be treated by ablative (radical diathermy, cryotherapy, or laser ablation) or excisional (loop electrosurgical excision procedure (LEEP), laser conisation, or cold knife cone [CKC] biopsy) treatment modalities[47].

It is important to be aware that not all women with histologically confirmed CIN2/3 need to undergo excisional treatment. Women who are pregnant should only undergo an excisional procedure if invasive disease is suspected and women that desire fertility should be counselled about the benefits and risks associated with treatment procedures versus observation[7]. Additionally, the management of young women (aged < 25 years) with CIN2 remains controversial and requires further investigation (Publication III). For this reason, clinical acumen and experience is imperative in managing women diagnosed with high-grade CIN, as inappropriate management could unnecessarily increase the risk of cervical cancer; however, overtreatment also has consequences and could lead to complications for the patient[7].

1.5.3 High-grade glandular lesions

ACIS (Table 2 (I)) occurs at a rate of 0.3 to 1.25 per 100,000 woman with Australian and international data show that its incidence is increasing[2]. Evaluation of women suspected with ACIS should include colposcopy, endocervical sampling, and targeted biopsy when appropriate[7]. Colposcopic detection of ACIS may be unreliable in some cases, as the anatomical placement of this abnormality may extend deep into the endocervical canal[43]. If ACIS is histologically confirmed, hysterectomy remains the preferred treatment option, but for women wishing to preserve fertility, conservative treatment (i.e. CKC biopsy or LEEP) may also be considered (publication II)[7].

1.5.4 Follow-up of women treated for high-grade epithelial cervical abnormalities

1.5.4.1 High-grade squamous lesions (CIN2/3)

Women treated for CIN2/3 are at increased risk of further high-grade disease and cervical cancer[44]. Disease recurrence may be attributable to inadequately treated disease or the further development of CIN. Recurrence rates tend to be high in the initial 6-12 months after treatment, remaining constant thereafter[44-46]. There is no evidence reporting that the risk of recurrence substantially declines at any definite point in time[44-46].

A major change in the management of HSIL abnormalities implemented in the 2005 NHMRC Guidelines is the "Test of Cure" (ToC). The ToC is a pathway by which women return to the recommended two-yearly screening interval following treatment for an HSIL[7]. The ToC treatment pathway for a woman treated for HSIL requires a

colposcopy and cervical cytology 4-6 months after treatment. Twelve months after the treatment, cervical cytology and HR HPV DNA testing should be conducted; these would need to be conducted every 12 months until the patient shows negative results for both tests on two consecutive occasions[7]. Currently, there is no evidence on how successful the adoption of this management pathway has been in Australia, and international research is in a preliminary phase (publication IV and V)[47-49].

1.5.4.2 Adenocarcinoma in situ (ACIS)

In Australia, optimal follow-up is yet to be defined for women treated for ACIS (who did not undergo a hysterectomy)[7]. However, the 2005 NHMRC Guidelines recommend, "follow-up cytology must include cytological sampling of the endocervical canal". In view of the uncertainties in treating women with ACIS conservatively, "follow-up after treatment is best undertaken using both colposcopy and cytology"[7].

1.6 The "Big Data Revolution"

"Big data" is a relatively new concept that is utilised to describe data so large and complex that it exceeds the computing capacity of most conventional systems that perform data analyses[50,51]. Huge amounts of data are generated from health-care sources such as electronic health records, health insurance claims and even smart phone applications that monitor patient health. "Big data" is the subject of intense interest as industry stakeholders and researchers recognise the huge potential in extracting data variables from existing systems. National governments are increasing their support to the 'big data revolution' by funding initiatives designed to develop and capitalise on 'big data' [51,52].

Health researchers have long realised the value in large administrative databases. These databases contain a wealth of information that can now be accessed in a timely and cost-efficient manner due to advancements in computing power and further development of analytical methodologies[53,54]. These advancements have further facilitated data linkage or integration processes that offer greater utility over using individual databases for health research. Most importantly, these developments have led to valuable unbiased scientific contributions and have ensured identifiable advances in population health initatives[54].

1.7 Administrative data characteristics and data linkage

1.7.1 Administrative data characteristics

Administrative databases that are used in health research are pre-existing datasets whose primary purpose is the storage of information routinely collected from the point of service. These databases typically cover large populations within a defined jurisdiction and can span years (if not decades) of service. The variables typically collected within these databases are dependent on the dataset, however, they will generally include:

- A unique patient identifier number
- Patient's demographic information (e.g. first name, surname, residential address, date of birth etc.)
- Clinical data (e.g. diagnostic code, procedural codes etc.)

Clinical registries are different to administrative databases, they are designed to routinely collect detailed clinical information to follow-up patients, ensure quality assurance standards are adhered to and can be readily accessed to support the development of evidence-based guidelines. In Australia, cervical screening registers (CSRs) fulfil many important roles. including[2]:

- Provision of a 'safety net' for women who have not had follow-up of an abnormal result.
- Provision of women's cervical screening histories to cervical cytology providers to allow a more detailed evaluation of present findings.
- Provision of data on the epidemiology and natural history of precancerous lesions.

These registers are powerful tools for researchers due to the level of detailed clinical information they contain that current administrative databases simply cannot match.

In WA, the CSR is an integral component of the WA Cervical Cancer Prevention Program (WACCPP). The WACCPP manages and operates the Register – a centralised database of Pap smear and follow-up tests, including cervical biopsy and HPV results. Data pertaining to cytology, histology, and HPV test results have been coded as per WACCPP codification sheets (Appendix 3, Appendix 4) and by lesion severity.

The CSR of WA has been operational since 1994 and participation to the Register is voluntary. Confidentiality of the data held is governed by legislation: *Health (Cervical Screening Register) Regulations 1991 (WA)*. Service providers are encouraged to inform women about the Register and if the woman does not object, the pathology laboratory will routinely forward the cervical screening test results (together with basic demographic information) to the Register. Currently (December 2014), the Register holds records of approximately 780,000 women screened in WA. Less than 0.5% of the women have requested that their information be removed from the Register since its inception in 1994.

1.7.2 Data linkage

Data linkage (or data integration) is defined as the "bringing together from two or more different data sources that relate to the same individual, family and/or place"[56]. This concept was first suggested in 1946, Dr Halbert Dunn who proposed the development of a "Book of Life"[57]. Within this book an individuals significant events would be recorded (i.e. birth, education, marriage, divorce, health history and death). This information would be collated for a population to assist in generating knowledge to further support health and welfare organisation's. Dr Dunn defined this collection process as 'record linkage'.

1.7.3 Data linkage techniques

The linkage of two or more datasets requires identifiers that are common to all datasets[57,58]. Such identifiers may be unique (e.g. patient's Medicare number), or partial (e.g. first name, surname, date of birth, gender etc.) and are matched using any of three general techniques.

1. Unique matching (deterministic matching) - data are linked according to unique identifiers (e.g. Medicare number). This would be the most expeditious way to link data; however, there are only a few datasets that share a common identifier limiting the potential data that can be linked. In addition, the potential for recording errors this method may only identify 80-85% of true matches[57].

2. Fuzzy matching – data are linked according to partial identifiers (usually multiple). This technique allows for margin by error by linking records that are almost the same. The computer will either present a choice of matches to the user or will rely on a scoring system to confirm a match. This usually identifies 85-90% of true matches[57].

3. Probabilistic matching – the decision regarding the match is made by

decision rules that are built into a software package. These are based on the probability that two records are from different people given they have the same identifiers. The probabilities are then aggregated to form a score and a link is confirmed if a predefined threshold is reached. This typically identifies 95-99% of true matches with a 1-2% false positive rate[56-58].

1.8 Benefits and limitations of administrative data for health research

Since research arising from administrative data is observational by nature there has been some scepticism regarding its value[59-60]. This is compounded by the heavy emphasis on randomized controlled trials (RCT) as the 'gold standard' for evaluating treatment, which ignores the limitations inherent in RCT methodology[59]. RCTs do not reflect real-life community practice, leaving clinicians to use their judgement in extrapolating findings from trials that relate to highly selected patients that is seldom encountered. Observational studies using large databases complement RCTs by going some way towards addressing their limitations[59]. Their large size provides whole-population capture; thereby avoiding non-representative samples and selection bias, which may occur in randomized trials. They measure the true effectiveness of an intervention that is based on actual 'real world' practice unlike the highly controlled RCTs environment. They are also better powered to study rare events and small effect size due to very large sample sizes, and the typically long time span covered by many databases enables long-term events to be examined. Recall bias and bias related to non-participation and loss to follow-up is minimised since all eligible people are included and, because these databases are primarily created for administrative purposes, individual patient consent is usually not required or warranted[54,63].

The advantages and social benefits of research arising from large administrative data and data linkage systems over traditional research methods are significant and include:

- Decreased cost of research; utilising existing data is relatively inexpensive and is an effective alternative to primary data collection[39,61].
- Increased efficiency of research: access to existing clinical information vastly reduces time compared to studies requiring primary data collection[62].
- Conservation of patient privacy: the privacy of individual patients is conserved since it is usually not required for personal identifiers to be provided to researchers[63]. Using de-identified administrative databases also

conserves the privacy of all patients, regardless of whether they would have given consent. A consent-based approach conserves the privacy only of those who do not participate, usually at a cost of making the research unachievable[64].

- Adding value to existing information assets: integrating datasets generates a greater return on investment in the original routine administrative data set and will facilitate quality improvement of data through the linkage process[66].

Limitations of studies using administrative data surround the use of data whose primary purpose is not for research[67]. The researcher should be cognisant of how the data was collected and coded. The first hurdle relies on the patient with a particular condition seeking care – if it is not serious enough to warrant seeking healthcare it will not be recorded and cannot be studied. There also needs to be a code attached to the condition or procedure of interest (usually International Classification of Diseases codes (ICD) e.g. ICD-10) and any additional uncoded clinical data cannot be studied.

Data quality and completeness will tend to vary across databases and variables being studied. Some errors are less likely to occur e.g. coding for primary surgical procedures; while others have been shown to be prevalent e.g. omitted coding for secondary diagnosis[66,67]. Databases may also change over time with changes in codes and the addition or deletion of variables. The way data is generated or collected may also vary between datasets and with time[66,67].

It is essential that researcher have a strong understanding and appreciation of how their data was generated and how it may have evolved over time. A close working relationship between researcher and data custodian is essential to avoid errors in analysis and interpretation. Validation studies with chart review can help quantify the size of these issues with any given data collection.

Finally, analysis of these databases should take into account the risk of confounding due to comorbidity, socio-demographic factors and effect modification[68]. Multivariate modelling techniques can be used to adjust for these effects so long as they are present within the data.

If these limitations are addressed in the study design, data analysis and interpretation, then any study finding can provide valuable additional information to existing evidence.

1.9 Data linkage in the Australian setting

The Population Health Research Network (PHRN) was established as a national network in 2009 to provide data linkage infrastructure across Australia as part of the National Collaborative Research Infrastructure Strategy. It is jointly funded by the Australian Commonwealth Government, State and Territory governments, universities and research institutes. The PHRN is project lead by the University of Western Australia and comprises a network of data linkage units that services each State and Territory in Australia and two national data linkage units for cross-jurisdictional linkages[69].

A unique feature of the PHRN is the development of the Secure Unified Research Exchange (SURE) by the Sax Institute. This purpose built remote-access data research laboratory allows researchers to work on approved data extracts through a virtual computer while data remains stored in a highly secured environment. SURE minimises the risk of privacy and confidentiality breaches since data are not stored on local computers/networks, improves accessibility of data to researchers and facilitates collaborations between researchers across multiple institutes[70].

The facilities and infrastructure developed by the PHRN make it unique worldwide since very few countries (notably the UK, Canada and some Scandinavian countries such as Sweden and Denmark) have the capability to perform population-based data linkage.

1.10 The WA Data Linkage System (WADLS)

1.10.1 Western Australian population

Western Australia covers a land area of 2.5 million square kilometres with a population of 2.5 million people[71]. Its capital city, Perth, is one of the most isolated cities in the world. The vast majority of the population (>70%) is located in the state's south-western corner and the remainder scattered sparsely across the state. The population is bordered by the Indian Ocean to the west and a vast expanse of desert to the east[72]. The relative geographical isolation minimises the degree to which women travel out-of-state to use health care services and creates a 'captive' population that is ideal for population-based research.

In 2010, Clark et al. confirmed that WA is ideal for population-based research and population-based research is representative of Australia[73]. Despite WAs isolation and only comprising of one-tenth of the national population, it is among three

jurisdictions that are closest to the eight-jurisdictional average, in six out of the eight socioeconomic and demographic indicators (i.e. proportion of privately insured and per capita health expenditure)[73]. Therefore the findings within this thesis are applicable to the wider Australian context.

1.10.2 The WADLS technology

The Data Linkage Branch within the WA Department of Health administers the WADLS[74]. The Data Linkage Branch uses computerised probabilistic matching based on best practice to create a dynamic master linkage key between more than 40 population-based administrative and research health data collection in WA[74]. The linkages mean that the total historical population (approximately 3.7 million people over more than 30 years) can be researched for all major diseases, disease risk factors and health service utilisation and outcomes[74].

The system is built on a foundation of nine core elements: birth, death and marriage registrations, hospital separations, midwives' and cancer notifications, mental health service encounters, emergency presentations and electoral roll registrations (Figure 3). A key aspect of the system design is the separation of linkage-related processes from those operating on sensitive clinical and service data. Thus, the WADLS is not a database repository but instead consists of pointers or indices to source data elements known as the *Master Linkage Key*[75]. The original data is maintained under the jurisdiction of the individual data custodian and only upon a formal data request is the data retrieved from the relevant custodian[76].

The WADLS is both retrospective and prospective, as it is updated routinely with the additional capability to create links within and between new external and internal data resources. Linkages are identified using probabilistic matching techniques[76], which are based on unit medical record number (unique only to public hospitals), full name and address, phonetic compression algorithms and demographic information such as date of birth, gender and postcode. Linkage to health related evens for individual subjects are ordered chronologically to form a 'chain of events'. These links are readily broken and re-joined to insert new links or delete incorrect ones allowing huge flexibility for expansion. Manual clerical checking is performed to search for possible matches in 'grey zones' between definite matches and non-matches[75].

Linkage accuracy has been well validated with the average proportion of invalid links (false positives) and missed links (false negatives) estimated as 0.11%[77]. An audit

conducted in 2001 and 2002, involving detailed clerical scrutiny of linked chains (in some cases up to 2,000 links), resulted in an estimate of <0.3% of chains with one or more incorrect links[78].

Figure 2   The Western Australian Data Linkage System
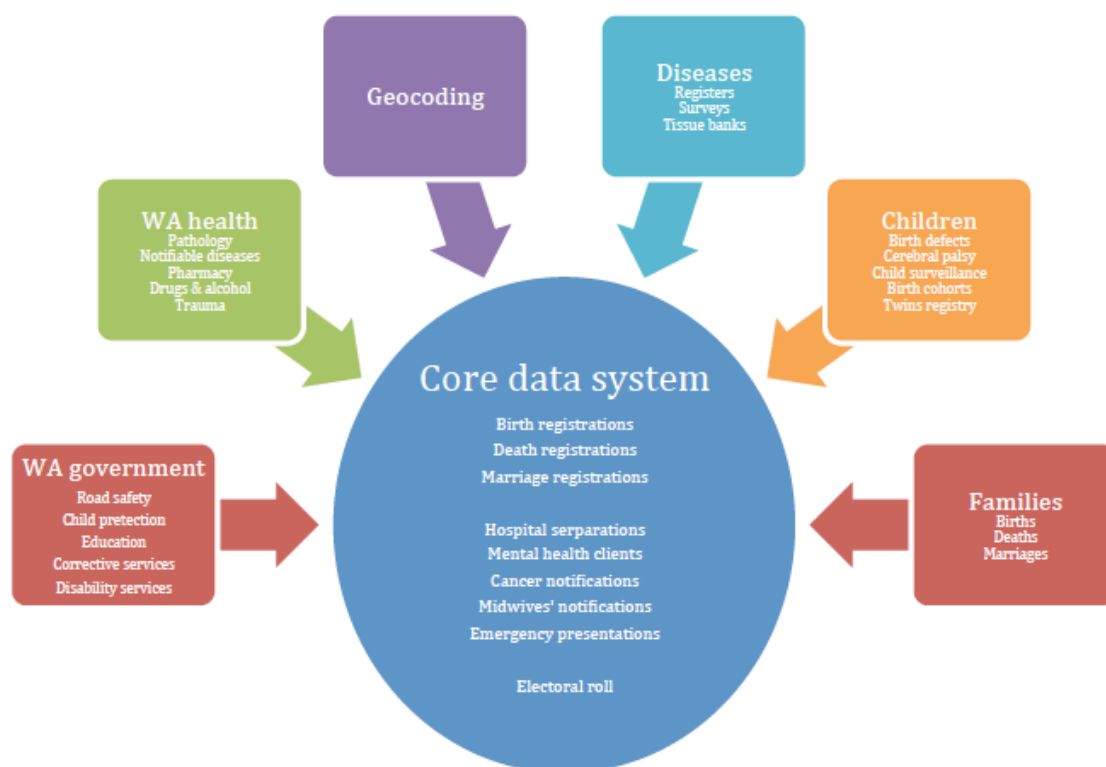
1.10.3 WADLS data access and privacy

In response to rising concerns for patient privacy there has been an increase in the legislative and regulatory requirements for access to linked health data for medical and health research. This has resulted in a broader system of protocols being developed progressively within the WADLS to address the concerns of consumers and data custodians with respect to privacy and data release[75].

Access to WADLS is granted only to researchers who have the appropriate Human Research Ethics Committee approvals to conduct their research and who have been granted permission by relevant data custodians. This ensures the data variables requested is appropriate for the proposed research. Strict protocols that have been

designed to protect confidentiality and security of the data must be followed and researchers are strongly encouraged to only use unidentifiable data[74].

Rather than increasing the risk of privacy within the community, it has been shown that the WADLS has significantly reduced the exposure of private and confidential personal health information in WA. This has occurred as access to personal details in linked data is confined to a small-specialised linkage group that adhere to rigorous, strict privacy and confidentiality requirements. As linked data sources have come online the requirement for named data in studies has declined dramatically from 90% in 1991 to 36% in 2003[63].

1.11 Published Manuscript

Munro A, Pavicic H, Leung Y, Westoby V, Steel N, Semmens J, O'Leary P. **The role of general practitioners in the continued success of the National Cervical Screening Program.** *AFP 2014*; 43(5): 293-6.

The role of general practitioners in the continued success of the National Cervical Screening Program

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Background

As the gateway to healthcare for Australian women, general practitioners (GPs) are critical to the success of the National Cervical Screening Program (NCSP). Despite an enviable record – halving the incidence and mortality of cervical cancer – in 2010–2011 more than 2.7 million women did not comply with the recommended 2-yearly screening interval.

Objective

General practice strategies are presented to assist GPs in encouraging all women, in particular, high-risk and vulnerable women, to participate in cervical screening.

Discussion

GPs play a crucial part in addressing the demographic, psychosocial and healthcare barriers that prevent women's participation in cervical screening. Encouraging uptake of the human papillomavirus vaccine and educating all patients on the importance of continued participation in cervical screening is essential for further decreasing the prevalence of this disease through early detection and treatment of cervical abnormalities.

Keywords

gynaecological; opportunistic; women's health

Human papillomavirus (HPV) infection is an extraordinarily common viral infection (11.4% of women in the general population are estimated to be infected at any given time[1]) and acquisition can occur rapidly after sexual debut.[2–4] Persistent infection by oncogenic HPV types is well recognised as a prerequisite for development of cervical cancer.[5,6] Consequently, many countries have implemented HPV vaccination and an organised approach to cervical screening.[7] Worldwide, 40 countries have HPV vaccination as part of their national immunisation schedule[8] and 15 have a systematic cervical screening program.[7]

HPV vaccines that protect against oncogenic HPV types 16 and 18, which are responsible for 70% of cervical cancers, have been available in Australia since 2007.[9] Preliminary investigations analysing the effect of the HPV vaccine are promising, although longitudinal population studies are needed to further investigate and validate the effectiveness of the vaccine.[9] HPV vaccination does not replace cervical screening because 30% of cervical cancer incidences are caused by other oncogenic HPV types that are not protected by the vaccine.[10] In Australia, all women are advised to continue having regular Pap smears whether or not they have been HPV vaccinated.[11] The National Cervical Screening Program (NCSP) has adopted an organised approach to cervical screening, which has halved cervical cancer mortality[12] (*Figure 1*). Despite Australia's two-pronged approach to preventing cervical cancer, 771 women were diagnosed in 2009 and in 2010, 232 women died from this largely preventable disease.[12] These incidence and mortality outcomes highlight the importance of women having routine (2-yearly) Pap smears, which can prevent up to 90% of the most common type of cervical cancer.[13]

Women's participation

In the general practice setting, about 1.7 per 100 encounters will be for a Pap smear.[14] Consequently, general practitioners (GPs) play an important part in providing information and services for women. GPs are well placed to encourage women to participate in cervical screening, including those with known cervical cancer risk factors, such as a history of multiple sexual partners, young age at first sexual intercourse, current tobacco use and immunosuppression (eg. HIV-positive).[15–18]

The continued success of the NCSP relies on sustaining a high rate of participation of eligible women (ie. those aged 20–69 years and with an intact cervix who have commenced sexual activity). In 2010–2011, 57.2% of eligible women participated in the NCSP at the recommended (2-yearly) interval, a significant decline from 63.4% in 1998–1999[12] (*Figure 2*). The Practice Incentives Program (PIP) for cervical screening offers financial incentives to encourage GPs to perform Pap smears on under-screened women aged 20–69 years.

Potential barriers

Unfortunately, the benefits of participation in cervical screening are not fully realised or shared equally by all women.[19] The reasons for women not participating in cervical screening and the impact of not participating are complex and multifaceted and,

therefore, difficult to quantify.[20–23] Previous studies report that a lower uptake of cervical screening by vulnerable populations (ie. women from an ethnic background or low socioeconomic status) may be associated with cultural beliefs, language barriers, lack of information regarding cervical screening benefits and prohibition by male partners.[22,24–29] Women often prefer a female practitioner to perform their Pap smear. This is particularly relevant for Aboriginal and Torres Strait Islander and culturally and linguistically diverse women.[31]

Different barriers exist at different stages of life. Studies have reported that menopausal and/or post-menopausal women may not realise that participation in cervical screening is required after the reproductive years.[26,27] Younger women (<25 years) have reported different barriers to participating in cervical screening including:

- being too busy to book an appointment[27]
- finding it difficult to book in for screening through the GP appointment systems[28]
- believing they are covered by the HPV vaccine and no longer need to have regular (2-yearly) Pap smears.[29]

A GP's approach to performing a Pap smear is critical in assisting women to overcome potential feelings of emotional unpleasantness, vulnerability, anxiety and fear.[24,25]

In 2011, the Western Australia Cervical Cancer Prevention Program (WACCPP) conducted a pilot study investigating women's attitudes, knowledge and understanding of cervical cancer prevention.[25] Participants included women aged 18–69 years (53% of participants were aged 31–54 years), living in the WA metropolitan area, with varying levels of education (Year 10 or lower, 23%; university qualification, 34%) and employment situations (full-time, 35% and home duties, 22%), who had ever been sexually active and had not had a hysterectomy. Thirty women were interviewed to investigate factors that contribute to reluctance or motivation to participate in cervical screening. Of particular relevance to GPs, the study found that participants request GPs to validate their emotions and to recognise that their feelings are not merely perception but are reality. If such acknowledgement occurs, it will support GPs in assisting their patients to make an empowered decision to have a Pap smear, rather than the patient simply following directions.[25]

Breaking down the barriers
Communication

Talking through concerns and addressing why the patient may feel uncomfortable and/or be avoiding cervical screening will promote the patient's commitment to overcoming perceived barriers and improve their adoption of preventive health behaviours. The WACCPP pilot study reported that 66% (n = 368) of participants knew 'not much/nothing' about cervical cancer.[25] Allowing adequate time with patients to provide them with information about the benefits and limitations of the Pap smear will break down the barriers to patients accessing a screening service.[30]

Before performing the Pap smear, the consultation should include advice on the implications of positive and negative test findings,
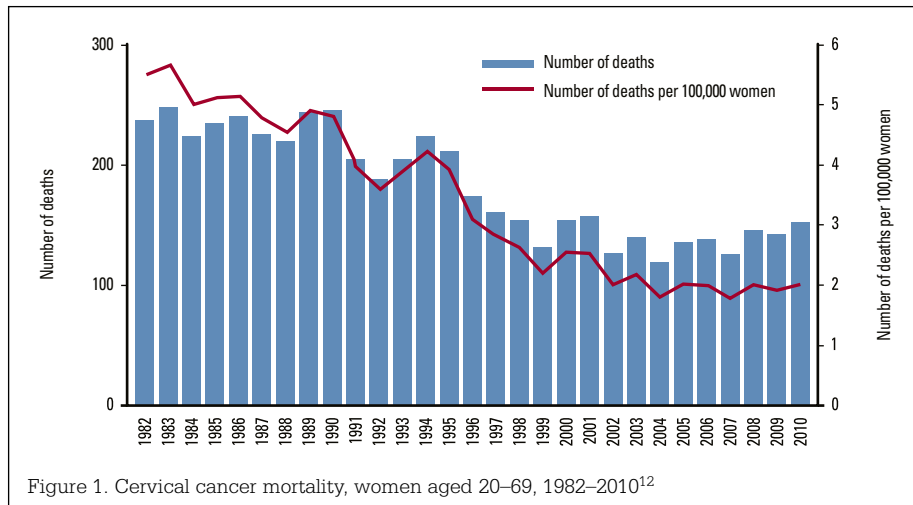

Figure 1. Cervical cancer mortality, women aged 20–69, 1982–2010[12]
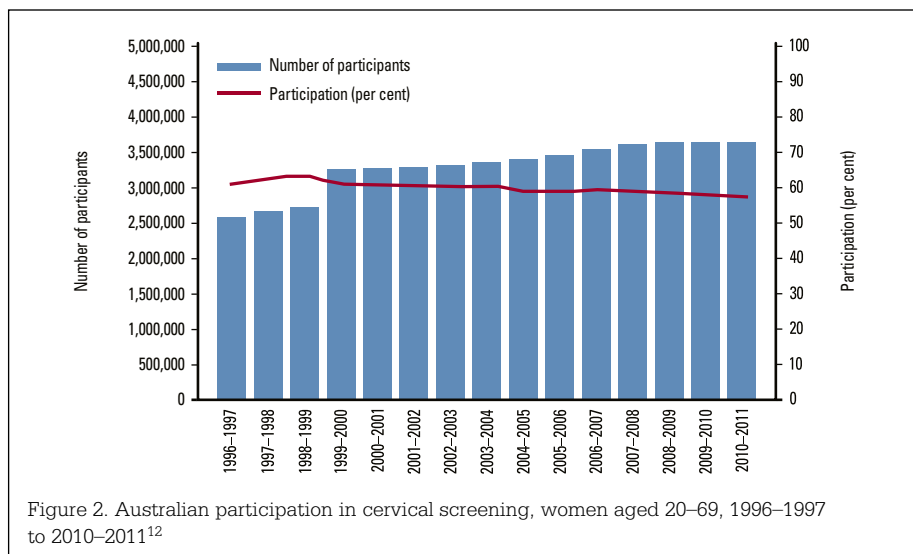

Figure 2. Australian participation in cervical screening, women aged 20–69, 1996–1997 to 2010–2011[12]

and a plan for communication of the test result.[31] In particular, a process whereby normal Pap smear results are provided over the phone has been shown to be helpful.[30,32–34]

Recall and reminder systems have mutual benefits for patients and GPs[35–37] by providing individual support to patients, promoting adherence to screening recommendations and improving continuity of care. Computerised patient record management software packages are available for use in practices and may assist GPs in having timely recall and reminder practice systems. Practices could use this software to identify patients who are due for screening, as well as those who are under-screening, and invite those patients to have a Pap smear. Australian cervical cytology registries complement general practice reminder services by providing a 'safety net' through contacting healthcare providers and the patient should they be overdue for their next cervical screening test.

Opportunistic screening

It is imperative that GPs opportunistically encourage women's participation in cervical screening. This is particularly important for women who are under-screened (have not had a Pap smear in the past 4 years) and can be achieved by identifying patients due for screening and encouraging eligible patients to have a Pap smear. Other strategies include educating patients about the screening pathway, when it is appropriate to commence and finish cervical screening, and offering a Pap smear during the consultation. Because of time constraints, these strategies may not always be feasible in the general practice setting. However, informing patients that they are due for their Pap smear and offering to make another appointment will serve to highlight the importance of cervical screening and encourage participation.

Delivery of screening services

Service delivery is critical, as communication alone will not result in sustained behaviour change. One of the most important strategies to ensure women's participation in cervical screening is providing accessible and acceptable screening services.[33,35–40] This can be achieved by offering patients a variety of clinic times (including facilitating booking appointments through email), offering bulk-billing for Pap smears and, where

possible, providing access to female Pap smear providers (eg. employing a female nurse/midwife who can perform cervical screening services). In this way, general practices can contribute to a reduction in social inequalities and improve access to cervical screening services.[30,41]

Promoting access to cervical screening can also be achieved by providing information about where patients can find practitioners whom they consider acceptable to perform the screening. It is important to have an awareness of:

- the Medicare Local
- local women's health centres
- Aboriginal medical services
- healthcare services for women with disabilities
- healthcare services for migrant and refugee women.

A patient who attends a different practitioner for Pap smears instead of her usual GP should be encouraged to have a copy of her cervical screening test result forwarded to her usual GP. This will assist in:

- supporting the patient with follow-up care if an abnormality is detected
- reminding the patient to re-screen at the appropriate interval.

Alternatively, with the patient's permission, the appropriate state or territory Cervical Cytology Registry can be contacted (13 15 56) to request the patient's most recent cervical test result.

Conclusion

GPs play a critical part in educating women on the benefits of the HPV vaccine and participating in routine cervical screening. Providing comprehensive education to women provides the GP with an opportunity to espouse a life course approach to cervical cancer prevention. Implementation of key strategies in general practice, such as provision of accessible services, recall systems and opportunistic screening, will ensure GPs continue to contribute to the success of the NCSP.

Key points

- Check eligibility for the PIP – Cervical Screening. Information can be found at www.medicareaustralia.gov.au/provider/incentives/pip/index.jsp
- Provide information (including posters, fact sheets, DVD's, brochures etc.) to support patients. These can be found on the National

Cervical Screening Program website at www.cancerscreening.gov.au

- Be aware that the NCSP is conducting a Renewal, a review of the science and technologies related to cervical cancer prevention. The Renewal will ensure that all Australian women have access to a cervical screening program that is based on the best available evidence and promotes best clinical practice. Information can be found at www.msac.gov.au/internet/msac/publishing.nsf/Content/1276

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Competing interests: None.

Provenance and peer review: Not commissioned; externally peer reviewed.

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Chapter 2:

Investigation of the clinical significance of cytologically detected endocervical (glandular) abnormalities

Research output

Published manuscripts

1. **Munro A,** Williams V, Semmens J, Leung Y, Stewart CJR, Codde J, Spilsbury K, Steel N, Cohen P, O'Leary P. **Risk of high-grade cervical dysplasia and gynaecological malignancies following the cytologic diagnosis of atypical endocervical cells of undetermined significance: A retrospective study of a state-wide screening population in Western Australia.** *A N Z J Obstet Gyn* 2015; 55(3): 268-73.

Conference presentations

1. **Munro A,** Williams V, Semmens JB, Leung Y, Stewart CJR, Codde J, Spilsbury K, Steel N, O'Leary P. **High-grade abnormality following the cytologic diagnosis of atypical endocervical cells of undetermined significance: A retrospective study of 1736 cases.** *15th Biennial Meeting of the International Gynecologic Cancer Society.* Melbourne, Australia, November 2014 (poster).
2. **Munro A,** Williams V, Semmens JB, Leung Y, Stewart CJR, Codde J, Spilsbury K, Steel N, O'Leary P. **High-grade abnormality following the cytologic diagnosis of atypical endocervical cells of undetermined significance: A retrospective study of 1736 cases.** *2014 World Cancer Congress.* Melbourne, Australia, December 2014 (poster).

2.1 Background

A variety of diseases affect the uterine cervix, of which glandular abnormalities comprise less than one-quarter[79]. As glandular abnormalities are uncommon, the acquisition of knowledge and clinical significance of these lesions has occurred slowly as compared to that of squamous lesions[2, 4, 79]. In 2004, the AMBS classification for cervical glandular abnormalities was revised because of our increasing understanding of the diagnostic importance of the range of endocervical changes observed in cytological specimens[7].

The revised low-grade glandular categories took into consideration indeterminate glandular cell changes without the features of ACIS. The revised low-grade glandular categories are [7]:

- *"Atypical glandular cells of undetermined significance is to be reported when the medical scientist/pathologist is unsure whether the affected cells are endocervical (site unknown)".*
- *"Atypical endocervical cells (AEC) of undetermined significance is to be reported when the medical scientist/pathologist is confident that the affected cells are endocervical (site known)".*

Currently, women diagnosed with AEC are referred to colposcopy with subsequent management dependent on the colposcopic and biopsy findings[7]. To date, no study has investigated the clinical outcomes for women with cytological findings of AEC and the risk of development of or of concurrent high-grade cervical disease, squamous or glandular. Consequently, Chapter 3 investigates women's health outcomes after a diagnosis of low-grade glandular lesions and addresses Objective 1. This thesis provides valuable insights into the clinical significance of AEC including associated health outcomes. Importantly, Publication 1 confirms that an AEC cytology test results definitively warrant further investigation.

2.2 Aim

Chapter 3 (Objective I) investigated the incidence of histologically confirmed high-grade cervical dysplasia (CIN2, CIN3 or ACIS), cervical carcinoma and endometrial carcinoma in women that presented with AEC on cervical cytology.

2.3 Methods

A population-based retrospective study examining the clinical outcomes of women with AEC detected on a screening cervical smear. Cytology and histology results were extracted from the Cervical Screening Registry (CSR) of Western Australia (WA). Time-to event analysis was used to predict the odds of having or developing in situ and/or invasive neoplasia.

2.4 Results

AEC was reported in index smears from 0.093% (584/622754) women during the study period. No follow-up data was available for 35 AEC cases. Sixty-six of the remaining 549 women (11.8%) had, or developed, high-grade cervical dysplasia within five years of their index AEC diagnosis. Endometrial cancer was diagnosed in 21 women and cervical cancer in four women during the follow-up period.

2.5 Conclusion

Cytologic demonstration of AEC requires careful gynaecologic evaluation, particularly in younger women who may be found to have either high-grade cervical lesions (CIN2, CIN3 or ACIS), while in older women, the possibility of endometrial neoplasia needs to be considered (Publication 1).

2.6 Published Manuscript

Munro A, Williams V, Semmens J, Leung Y, Stewart CJR, Codde J, Spilsbury K, Steel N, Cohen P, O'Leary P. **Risk of high-grade cervical dysplasia and gynaecological malignancies following the cytologic diagnosis of atypical endocervical cells of undetermined significance: A retrospective study of a state-wide screening population in Western Australia.** *A N Z J Obstet Gyn* 2015; 55(3): 268-73.

Original Article

Risk of high-grade cervical dysplasia and gynaecological malignancies following the cytologic diagnosis of atypical endocervical cells of undetermined significance: A retrospective study of a state-wide screening population in Western Australia

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Background: In 2006, Australia adopted a revised cervical cytology terminology system, known as the Australian Modified Bethesda System (AMBS). One substantial change in the AMBS was the introduction of the diagnostic category of atypical endocervical cells (AEC) of undetermined significance.

Aim: The aim of this study was to investigate the incidence of histologically confirmed high-grade cervical dysplasia (cervical intra-epithelial neoplasia (CIN) grades 2 and 3 and adenocarcinoma *in situ* (ACIS)), cervical carcinoma and endometrial carcinoma in women presenting with AEC on cervical cytology.

Methods: A seven-year retrospective study examining clinical outcomes of women with AEC on a screening cervical smear. Cytology and histology results were extracted from the Western Australia Cervical Screening Registry, and time-to-event analysis was used to predict the odds of having or developing *in situ* and invasive neoplasia.

Results: AEC was reported in index smears from 0.093% (584/622754) women during the study period. No follow-up was available in 35 AEC cases. Sixty-five of the remaining 549 women (11.8%) had, or developed, high-grade cervical dysplasia within five years of their index AEC diagnosis. Endometrial cancer was diagnosed in 21 women and cervical cancer in four women during the follow-up period.

Conclusion: Cytologic demonstration of AEC requires careful gynaecologic evaluation, particularly in younger women who may be found to have either high-grade squamous (CIN) or glandular (ACIS) lesions, while in older women, the possibility of endometrial neoplasia needs to be considered.

Key words: atypical endocervical cells, atypical glandular cells, cervical cancer, cervical cytology, cervical screening, endometrial cancer, Papanicolaou smear.

Introduction

The incidence of and mortality from cervical cancer (specifically squamous carcinoma) has been reduced in many countries as a result of cytology screening using the Papanicolaou (Pap) smear,[1–5] but significant challenges remain. In particular, there has not been a substantial reduction in the number of invasive glandular neoplasms (adenocarcinomas), which now represent up to 20% of all cervical malignancies.[1,6] Compared to squamous lesions, endocervical (glandular) abnormalities are more likely to be under-diagnosed cytologically and the role of the Pap smear in identifying asymptomatic women with high-grade pre-invasive glandular neoplasia (adenocarcinoma *in situ*, ACIS) is less clearly defined.[6] This may be partly attributable to sampling error, given the anatomical distribution of the endocervical epithelium, and may also reflect the diagnostic difficulties encountered by cytopathologists when interpreting the relatively rare glandular lesions.[1,6–8]

Atypical endocervical cells (AEC) of undetermined significance is an uncommon cervical cytology finding, being reported in less than 1% of Pap smear tests.[1] Atypical endocervical cells are reported when the medical scientist/pathologist is confident that the affected cells are endocervical. These smears demonstrate changes in glandular cells that are considered beyond those typical of a reactive process but insufficient for a confirmed diagnosis of endocervical neoplasia (ACIS or adenocarcinoma).[9] Several studies have demonstrated that AEC may be associated with premalignant or malignant cervical lesions but most have been limited by short follow-up periods and/or relatively small numbers of cases.[7,10–12] Furthermore, the risk of significant pathology has not always been correlated with age, prior smear history, presence of endocervical cells in preceding cytology samples or the socio-economic status of the patient. In the present study, we have investigated the potential relationship between these factors and the risk of high-grade cervical dysplasia and gynaecological malignancies in women with a cytological diagnosis of AEC in Western Australia (WA) over a seven-year period.

Materials and Methods

Study design

This is a retrospective cohort study of women with an index Pap smear demonstrating AEC during the period 1 January 2006 to 31 December 2012 in WA. Study data were obtained in June 2013 following approval from the Curtin University Human Research Ethics Committee (ethics research project number: HR 86/2012).

Source of data

As part of the National Cervical Screening Program (NCSP), the Western Australian Cervical Cancer Prevention Program (WACCPP) encourages eligible women (women aged 20–69 years that have not had hysterectomy and have commenced sexual activity) to undergo a screening Pap smear every two years. The WACCPP maintains the Cervical Screening Register (CSR) of WA which compiles the results of Pap smears and related diagnostic tests from all laboratories in WA; reporting of these data is a legislative requirement. The CSR is an opt-out system and <0.1% of women request that their results be excluded. A de-identified data set was extracted from the CSR of cervical screening histories for all women residing in WA who presented with AEC during the study period.

Women were allocated measures of socio-economic status using the Socio-Economic for Indexes for Areas (SEIFA) for Australia obtained through the Australian Bureau of Statistics.[13] Additionally, women's postcodes were assigned to one of four Accessibility/Remoteness Index of Australia levels based on their SEIFA values.[14] Due to small numbers, remote and very remote postcodes

were collapsed into one category for the purposes of this study.

Classification of cytology and histology results

Cervical cytology results were classified in accordance with the Australian Modified Bethesda System (AMBS) 2004 which is directly comparable to the Bethesda System 2001 (Table 1).[9] Histologically, the high-grade cervical lesions included cervical intra-epithelial neoplasia (CIN) grades 2 and 3, ACIS and cervical carcinoma (all types). For primary endometrial abnormalities, only cases with a diagnosis of endometrial carcinoma (all types) were recorded. Endometrial hyperplasia data were not available within this study cohort. All histology results were classified according to the highest grade abnormality identified.

Inclusion and exclusion criteria

Only women aged 18–75 years with index cervical cytology showing AEC (with a normal, low-grade or possible low-grade squamous component) were included in this study. Exclusion criteria included: (i) any prior screening history of a high-grade abnormality; (ii) previous histological confirmation of low- or high-grade CIN or invasive cervical cancer; (iii) hysterectomy; and (iv) no available follow-up data.

Management pathway following AEC

Women were managed in accordance with the 2006 NHMRC Guidelines which recommend that women with AEC be referred directly for colposcopy.[9] Women with normal colposcopy usually would be managed conservatively with repeat cytology and colposcopy at six months whereas women with abnormal colposcopic findings generally underwent diagnostic biopsy.[9]

Australian cervical cytology registries do not routinely collect colposcopy data; however, the CSR of WA does record the practitioner's status (ie a specialist code for gynaecologist, gynaecologist/oncologist), and therefore, this study was able to determine whether women had further investigation under the care of a specialist.

Correlative analyses

Time-to-event analyses were performed to investigate the risk factors associated with a subsequent high-grade cervical lesion after the cytological diagnosis of AEC. This was not performed with the cervical or endometrial cancers in view of the small number of cases. The follow-up interval was defined as the time from the index AEC test until the diagnosis of a high-grade lesion histologically or the study censor date (the last cervical smear result).

Covariates included in the time-to-event analysis were age, socio-economic status, an index of accessibility to services, Pap smear screening history and calendar period.

Table 1 The Bethesda System (2001) and Australian Modified Bethesda System (AMBS) (2004) classification of cervical cytology abnormalities[9]

The Bethesda System	AMBS 2004	Incorporates
Squamous abnormalities		
Atypical squamous cells, undetermined significance (ASC-US)	Possible low-grade squamous intra-epithelial lesion	Nonspecific minor squamous cell changes. Changes that suggest, but fall short of, HPV/cervical intra-epithelial neoplasia (CIN) 1
Low-grade squamous intra-epithelial lesion	Low-grade squamous intra-epithelial lesion (LSIL)	HPV effect, CIN 1
Atypical squamous cells, possible high-grade lesion (ASC-H)	Possible high-grade squamous intra-epithelial lesion	Changes that suggest, but fall short of, CIN 2, CIN 3 or squamous cell carcinoma
High-grade squamous intra-epithelial lesion (HSIL)	High-grade squamous intra-epithelial lesion (HSIL)	CIN 2, CIN 3
Squamous cell carcinoma	Squamous cell carcinoma	Squamous cell carcinoma
Glandular abnormalities		
Atypical endocervical cells of undetermined significance	Atypical endocervical cells of undetermined significance	Nonspecific minor cell changes in endocervical cells
Atypical glandular cells of undetermined significance	Atypical glandular cells of undetermined significance	Nonspecific minor cell changes in glandular cells
Atypical endocervical cells, possibly neoplastic	Possible high-grade glandular lesion	Changes that suggest, but fall short of, AIS or adenocarcinoma
Endocervical adenocarcinoma in situ	Endocervical adenocarcinoma in situ	Adenocarcinoma in situ
Adenocarcinoma	Adenocarcinoma	Adenocarcinoma

Table 2 Summary of demographic details

Characteristics	n = 549	Percentage
Age at index smear (years)		
≤24	52	9.5
25–34	111	20.2
35–44	162	29.5
45–54	153	27.9
≥55	71	12.9
Previous screening interval prior to index AEC (years)		
Never screened	77	14.0
≤1 and required follow-up	43	7.8
<1 year early rescreen	39	7.1
>1 year although required follow-up	16	2.9
≥1- 4 years	321	58.5
>4 years	53	9.7
Endocervical component present in Pap smear prior to AEC?		
Yes	379	69.0
No	93	16.9
No Pap smear	77	14.1
Number of women than underwent specialist evaluation		
Yes	456	83.1
No (repeat Pap smear)	93	16.9

The interval between the index AEC smear and the preceding cervical cytology was calculated, and the screening history was categorised as outlined in Table 2. It was also noted whether the preceding cytology sample included endocervical cells.

Statistics

Kaplan–Meier graphs were constructed to investigate the survivorship function (time until biopsy-confirmed high-grade cervical lesion or malignancy), and log-rank tests were used to assess equality of the survivorship function. Parsimonious proportional hazards models were constructed to investigate the relative rate (hazard rate) of having, or subsequently, developing a high-grade cervical lesion postindex AEC after simultaneously adjusting for multiple factors. Models were constructed using purposeful selection of covariates. Violation of the proportional-hazard assumptions was assessed, and biologically plausible interaction terms between variables were tested. The 95% confidence intervals (CI) for the hazard rate ratios were also calculated. STATA/IC 13.0 (STATA Corporation, College Station, TX, USA) was used for statistical analysis.

Results

During the study period, 3,237,906 cervical smears were performed on 622,754 women. Of these, 584 women (0.1%) with no previous history of histologically confirmed low- and/or high-grade cervical lesions had AEC. Thirty-five women were excluded from further analysis as follow-up data were unavailable. For the remaining 549 women, the mean age at index AEC smear was 41.4 years (range 18–75 years) and the median follow-up was 1.9 years (range <1–6.8 years). Baseline characteristics of the cohort are presented in Table 2.

Table 3 Histological abnormality (highest grade lesion) according to age

	Age group (years)					
	≤24	25–34	35–44	45–54	≥55	Total
Histology outcomes						
Unsatisfactory	0	0	0	0	2	2
Negative	8	30	75	72	24	209
Low grade★	9	7	17	10	6	49
High-grade intra-epithelial lesions						
CIN 2	0	3	6	1	0	10
CIN 3	3	9	5	1	0	18
ACIS	6	20	10	1	1	38
Cervical malignancy						
Adenocarcinoma	0	2	0	1	0	3
Adenosquamous carcinoma	0	1	0	0	0	1
Endometrial malignancy						
Endometrial carcinoma	0	0	1	6	14	21
Total	26	72	114	92	47	351

★Low grade includes Atypia – atypical immature squamous neoplasia, HPV effect, Mild dysplasia (CIN I).

Of this patient cohort, 198 women were managed conservatively with repeat cytology; 105 (53%) of these women were under the care of a specialist who performed the cytology test. No high-grade lesions were identified on follow-up of this cohort. The remaining 351 women underwent biopsy within 24 months of the AEC smear. The histological findings for the subset of women who underwent biopsy (*n* = 351) are summarised in Table 3. Ninety-one (25.9%) demonstrating high-grade abnormalities, including 28 (8.0%) CIN 2/3, 38 (10.8%) ACIS, 4 (1.1%) cervical carcinoma and 21 (6.0%) endometrial carcinoma.

Of the women diagnosed with endometrial cancer, the majority (66.7%) of cases occurring for women aged ≥55 years (Table 4). The median follow-up time from index AEC to endometrial diagnosis was 0.2 years (range <1 month to 6 years). All women with endometrial cancer had a hysterectomy performed.

Younger women were more likely than older women to have high-grade cervical lesions, particularly within the first three to four years postindex AEC smear (Table 4). The probability of remaining high-grade lesion free five years postindex AEC was 66% (95% CI 0.5–0.7) for patients aged 25–34 years (*P*-value = 0.003) compared to 97% (95% CI 0.9–1.0) for patients aged 45–54 years (*P*-value = 0.001). Age at AEC result remained strongly associated with the risk of developing a high-grade lesion even after adjusting for other covariates (Table 4). Women aged 25–34 years were at higher risk of developing high-grade lesions (HR 2.3) compared with women aged 35–44 years.

Compared to women with previous normal cervical screening, women with a previous low-grade abnormality and those with no prior screening history were also at increased risk of developing a high-grade lesion (Table 4). There was no correlation between socio-economic status, accessibility to services, the presence or absence of endocervical cells in the preceding cervical smear and the risk of developing a high-grade cervical lesion.

Discussion

To our knowledge, this is the first Australian study to investigate the clinicopathological correlations of AEC on cervical cytology since the AMBS introduced this diagnostic category in 2006.[9] Advantages of this study include the large size (584 cases) and population-based nature of the patient cohort together with a relatively long follow-up period of up to 6.8 years. Furthermore, by performing extensive data matching review, the CSR of WA was able to accurately determine clinical outcomes, including subsequent cervical cytology and histopathology findings in the great majority (94%) of cases.

The present study confirmed the low incidence (1%) of AEC in routine Pap smears. However, similar to earlier

Table 4 Hazard ratios of confirmed cervical high-grade lesion postindex atypical endocervical cells (AEC) smear according to age, screening history and date of index smear

	Hazard rate ratio	95% CI	*P*-value
Age (years)			
≤24	1.2	0.5–2.7	0.649
25–34	2.3	1.3–4.0	0.003
35–44 (reference group)	1.0		
45–54	0.1	0.1–0.5	0.001
≥55	0.1	0.1–1.1	0.059
Importance of screening interval prior to index AEC (years)			
Never screened	2.5	1.4–4.6	0.003
≤1 and required follow-up*	2.7	1.2–6.2	0.015
≤1 year early rescreen	0.8	0.2–3.4	0.748
≥1 year although required follow-up*	3.1	1.1–9.0	0.033
≥1–4 years no follow-up was required (reference group)	1.0		
≥4 years	1.7	0.7–4.0	0.199

investigations, we found that a significant minority of patients (12%) had, or subsequently developed, high-grade cervical dysplasia (CIN 2/3 or ACIS), and cervical and endometrial carcinomas were identified in a further 0.7 and 3.8% cases, respectively. In addition, 8.9% of patients had a biopsy-confirmed low-grade squamous abnormalities, including HPV changes or CIN 1 that would require closer cytological surveillance. Thus, the presence of AEC requires careful gynaecological evaluation.

While the cytological diagnosis of AEC implies an abnormality in endocervical cells, like earlier reports we found that a significant proportion of *in situ* cervical neoplastic lesions proved on histology to be of squamous (CIN) rather than endocervical (ACIS) type. This illustrates the cytological difficulty in distinguishing squamous and glandular lesions in some instances, particularly when cellular material is limited or poorly preserved, or when CIN involves endocervical crypts.[15,16] Similarly, most adenocarcinomas identified in this series were of endometrial rather than endocervical origin. It is well recognised that the distinction of endocervical and endometrial carcinoma can be problematic even on biopsy material, sometimes necessitating additional immunohistological studies for resolution.[17]

We found that the risk of high-grade cervical dysplasia was greater in younger women (aged 25–34 years), and in those with no cervical screening history or a previously detected low-grade cytological abnormality. In contrast, there was no correlation with socio-economic status or with access to services. Such factors could be taken into account in stratifying patient management, including the type or time interval for follow-up. There was also no correlation between the detection of high-grade dysplasia and the presence of endocervical cells in the cervical smear preceding the index AEC smear. This may be partly explained by the significant proportion of lesions ultimately classified as being of nonendocervical type, as discussed above.

In the present study, 4.8% of patients with AEC had invasive malignancies and the majority were endometrial cancers in women aged >45 years. Indeed, 30% of patients aged ≥55 years with AEC proved to have endometrial carcinoma. To our knowledge, there is no other Australian or international study that is directly comparable to the data presented in this study. Study comparisons are challenging due to previous Australian studies being conducted prior to implementation of the AMBS (2004) and in the majority of cases having grouped together AEC with other glandular abnormalities (ie endometrial and ovarian abnormalities).[18,19] Whilst Mitchell (2004)[20] reported on minor nonspecific changes of glandular cells, the results presented here are still noncomparable due to the classification changes.

Regardless, the present study demonstrates the requirement to exclude significant endometrial pathology in older women presenting with AEC. It is also worth noting that our study did not include patients who would be considered at increased risk of endometrial malignancy such as those with histologically documented endometrial hyperplasia.

Recently Australia's Medical Services Advisory Council recommended that the NCSP should move towards five yearly screening using primary HPV testing with partial HPV genotyping and reflex liquid-based cytology triage.[21] This is potentially beneficial in that HPV testing should identify most cervical neoplasms (*in situ* or invasive) and could help to differentiate cervical from noncervical lesions. However, it should be noted that not all cervical adenocarcinomas (or their precursors) are HPV-related,[22] and women with a cytological diagnosis of AEC will still require thorough investigation.

In summary, the present study supports the current recommendation that women with AEC on a cervical smear be referred for colposcopic examination. In general, further management will be dictated by the findings at colposcopy and/or biopsy, but more intense follow-up may be appropriate in younger women and in those with no previous cervical screening or with previous low-grade cytological abnormalities. Conversely, in older patients (particularly those aged ≥55 years), endometrial sampling is indicated in view of the risk of endometrial carcinoma.

Acknowledgements

Disclosure of interests

Two authors (A Munro and N Steel) are employed at the WA Cervical Cancer Prevention Program and are responsible for maintaining and operating the Cervical Screening Registry of WA.

Ethical Approval

Study data were obtained in June 2013 following approval from the Curtin University Human Research Ethics Committee (ethics research project number: HR 86/2012).

Funding

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Chapter 3:

Investigation of the effectiveness of conservative treatment for high-grade endocervical (glandular) abnormalities

Research output

Published manuscripts

1. **Munro A,** Leung Y, Spilsbury K, Semmens J, Codde J, O'Leary P, Williams V, Steel N, Cohen P. **Comparison of cold knife cone biopsy and loop electrosurgical excision procedure in the management of cervical adenocarcinoma in situ: What is the gold standard?** *Gynecol Oncol* 2015; 137(2): 258-63.

Conference presentations

1. **Munro A,** <u>Leung Y</u>, Spilsbury K, Semmens J, Codde J, O'Leary P, Williams V, Steel N, Cohen P. **CKC or LEEP for ACIS? What is the Gold Standard?** *2015 Australian Society of Gynaecologic Oncologists Scientific Meeting*. Penang, Malaysia, July 2015 (conference presentation).

3.1 Background

The treatment options for women with histologically confirmed ACIS remain controversial globally and there is a lack of reliable data to support the development of evidence-based management. In Australia, conservative treatment of ACIS by CKC biopsy is the "gold standard"[7]. CKC is currently preferred, as it appears to achieve more success with negative margins within the cone specimen. However, this procedure comes with the risk of complications, specifically for women desiring fertility preservation. CKC complications may include antagonistic obstetric outcomes such as second trimester miscarriage or pre-term delivery[30, 79]. Unfortunately, the majority of ACIS studies to date have been institutional reviews with a small number of cases and short follow-up intervals[80-82]. Furthermore, studies investigating the efficacy of other ACIS treatment modalities are limited[83-86].

Further epidemiological studies that report health outcomes of women treated conservatively (i.e. not with hysterectomy) for ACIS are required. The results of this work contributed to one of the first publications to explore this question. This is particularly important given that evidence-based management for glandular abnormalities of the cervix guidelines are lacking and the incidence of ACIS and invasive adenocarcinoma continues to increase, especially amongst young women. Therefore, the efficacy of adopting a conservative treatment approach for women with biopsy-confirmed ACIS were compared within Chapter 3 (Objective 2). Publication IV provides clinicians with clinical management recommendations for patients wishing to preserve their fertility.

3.2 Aim

The outcomes of patients with ACIS treated with CKC biopsy or LEEP for the treatment of ACIS were compared in Chapter 3 (Objective 2).

3.3 Methods

This is a retrospective, population-based cohort study of Western Australian patients with ACIS diagnosed between 2001 and 2012. Health outcomes included the patient's pathological margin status and the incidence of persistent or recurrent endocervical neoplasia (ACIS and adenocarcinoma) during follow-up (<12 months) and surveillance (≥12 months) periods.

3.4 Results

The study group comprised 338 patients including 107 (32%) treated initially by LEEP and 231 (68%) treated by CKC biopsy. Overall, 27 (8.0%) patients had ACIS persistence/recurrence while 9 (2.7%) were diagnosed with adenocarcinoma during the follow-up and surveillance periods. No patient died of cervical cancer within the study period.

There were no significant differences in the incidence of persistent and/or recurrent endocervical neoplasia according to the type of excisional procedure.

3.5 Conclusion

LEEP and CKC biopsy appear equally effective in the treatment of ACIS for women wishing to preserve fertility (Publication 2). Patients undergoing conservative management for ACIS should be closely monitored, particularly if biopsy margins are positive in initial excision specimens. Patients and their clinicians should be aware of the potential risks of residual and recurrent disease.

3.6 Published Manuscript

Munro A, Leung Y, Spilsbury K, Semmens J, Codde J, O'Leary P, Williams V, Steel N, Cohen P. **Comparison of cold knife cone biopsy and loop electrosurgical excision procedure in the management of cervical adenocarcinoma in situ: What is the gold standard?** *Gynecol Oncol* 2015;137(2): 258-263.
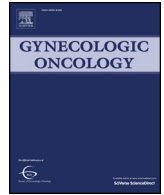
Comparison of cold knife cone biopsy and loop electrosurgical excision procedure in the management of cervical adenocarcinoma *in situ*: What is the gold standard?

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HIGHLIGHTS

• Women treated for ACIS by cold knife cone biopsy or LEEP were monitored for disease persistence.
• There was no difference in ACIS disease persistence between CKC and LEEP after 3.6 years of follow-up.

ARTICLE INFO

ABSTRACT

Objective. To compare the outcomes of patients with cervical adenocarcinoma *in situ* (ACIS) treated with cold knife cone (CKC) biopsy or loop electrosurgical excision procedure (LEEP) for the treatment of cervical adenocarcinoma *in situ* (ACIS).

Study design. This is a retrospective, population-based cohort study of Western Australian patients with ACIS diagnosed between 2001 and 2012. Outcomes included pathological margin status and the incidence of persistent or recurrent endocervical neoplasia (ACIS and adenocarcinoma) during follow-up (<12 months) and surveillance (≥12 months) periods.

Results. The study group comprised 338 patients including 107 (32%) treated initially by LEEP and 231 (68%) treated by CKC biopsy. The mean age was 33.2 years (range 18 to 76 years) and median follow-up interval was 3.6 years (range <1 year to 11.8 years). Overall, 27 (8.0%) patients had ACIS persistence/recurrence while 9 (2.7%) were diagnosed with adenocarcinoma during the follow-up and surveillance periods. No patient died of cervical cancer within the study period. There were no significant differences in the incidence of persistent and/or recurrent endocervical neoplasia according to the type of excisional procedure. Patients with positive biopsy margins were 3.4 times more likely to have disease persistence or recurrence.

Conclusion(s). LEEP and CKC biopsy appear equally effective in the treatment of ACIS for women wishing to preserve fertility. Patients undergoing conservative management for ACIS should be closely monitored, particularly if biopsy margins are positive in initial excision specimens. Patients and their clinicians should be aware of the potential risks of residual and recurrent disease.

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1. Introduction

The incidence of cervical cancer in developed countries has decreased significantly in the past few decades largely due to the adoption of public health screening programmes, but this mainly reflects a decrease in squamous cell carcinoma [1–3]. By contrast, the incidence of cervical adenocarcinoma has increased in both relative and absolute terms, and now represents 20–25% of all cervical cancer cases [1–3]. The recognised precursor to cervical adenocarcinoma is adenocarcinoma *in situ* (ACIS), and this frequently coexists with high-grade squamous intraepithelial neoplasia (CIN) and/or squamous cell carcinoma [4–6]. Cervical cytology is generally less sensitive in the detection of cervical glandular abnormalities compared to CIN,

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and it is reported that ACIS may also evade detection at colposcopy [7–10].

Conservative management of women with ACIS is controversial since these lesions can persist/recur and may co-exist with, or progress to, cervical adenocarcinoma [5,6,11]. Consequently hysterectomy is regarded as the definitive treatment [12,13]. However, ACIS commonly affects young women who may wish to preserve fertility and therefore local excisional procedures such as cold knife cone (CKC) biopsy or loop electrosurgical excision procedure (LEEP) have been utilized as alternatives to hysterectomy [6,7,11–14].

In Australia, CKC is regarded as the 'gold standard' treatment for ACIS [12]. There is a perception that there is a greater likelihood of incomplete excision with LEEP because the depth of excised tissue and the overall dimensions of the specimen tend to be smaller in comparison to CKC. It is also argued that the tissue margins in a LEEP biopsy may show significant thermal artefact, which can interfere with the pathological assessment of biopsy margins [15,16]. Some studies have shown a greater risk of a positive endocervical margin with LEEP but these have included cases in which ACIS was not suspected prior to the excisional procedure [17–19]. Conventional management has also been challenged by recent data which suggest that the risk of positive margins and disease recurrence are equivalent following LEEP or CKC biopsy [6,11]. Such findings could potentially alter treatment guidelines since accepted advantages of LEEP include the avoidance of general anaesthesia, provision of treatment in an outpatient setting, lower morbidity, and reduced rates of obstetric complications, all of which have significant cost benefits [6,11,19–23].

Nevertheless, the efficacy of conservative treatment of ACIS remains uncertain since most studies to date have been limited by small sample size and short follow-up [6,7,17–19]. In the present study we have determined the rates of residual and recurrent endocervical neoplasia in a large, population-based cohort of women in Western Australia (WA) who had conservative management of ACIS. Outcomes were correlated with patient age and socioeconomic background, type of excisional procedure, margin status, and the presence of concurrent high grade CIN.

2. Methods

2.1. Data sources and linkage procedure

The Cervical Screening Register (CSR) of WA is required by legislation to compile all cervical test results (human papillomavirus (HPV) detection, cytology and histology) for women who reside in WA. The CSR is an 'opt out' register and less than 0.05% of women request removal of their demographic information and results. The WA Data Linkage System (WADLS) provided a de-identified extraction of linked cancer registrations and death records for all women with ACIS identified by the CSR of WA from 2001 to 2012. The WADLS is an internationally renowned, population-based, validated and ongoing data linkage system that creates links among a number of state health administrative data sets [24–26].

Follow-up data were available up to May 2013. Death records were used to verify the number of cervical cancer related deaths and to censor women who died during follow-up. Study data were obtained following approval from the Curtin University Human Research Ethics Committee (ethics research project number: HR 86/2012) and the Western Australian Department of Health Human Research Ethics Committee (ethics research project number: 2012/49).

2.2. Participants

The CSR was used to identify women aged 18 years or older who were reported to have ACIS on either routine cervical cytology screening or on cervical punch biopsy. Only women who had histological confirmation of ACIS following CKC or LEEP biopsy were included in the study. Patients were excluded if they had prior histological documentation of CIN or cervical cancer. Cervical cytology was classified according to the Australian Modified Bethesda System 2004 [12]. Patient age at the time of treatment was classified as ≤30 years or >30 years. Postcode of residence was used to assign a socioeconomic level using the Australian Bureau of Statistics 2006 Socio Economic Indexes for Areas (SEIFA) [27]. Patients underwent CKC or LEEP procedures according to the surgeon's standard practice.

2.3. Histopathology findings

The following biopsy findings were determined from review of the histopathology reports: the type of biopsy (CKC or LEEP), depth of the specimen (measured macroscopic extent along the cervical canal), presence of concurrent CIN and resection margin status. The latter was considered 'positive' if any margin (ectocervical, endocervical or deep/circumferential) was involved by ACIS, 'negative' if all margins were histologically clear, and 'indeterminate' if margins could not be assessed or were not documented.

2.4. Follow-up

Management following the initial CKC biopsy or LEEP was determined. Subsequent management potentially included cytological review, repeat CKC biopsy or LEEP, or hysterectomy. The follow-up period was defined as the date of the initial ACIS treatment to the date of the last follow-up procedure (e.g., cervical cytology, biopsy or hysterectomy).

2.5. Principal outcomes

The principal outcomes investigated were i) persistence of ACIS or diagnosis of adenocarcinoma during the follow-up period (defined as disease detection <12 months after the initial diagnosis), and ii) recurrence of ACIS or diagnosis of adenocarcinoma within the surveillance period (defined as disease detection ≥12 months after the initial diagnosis). Cancer mortality was a secondary outcome measure.

2.6. Statistics

STATA/IC 13.0 (STATA Corporation, College Station, USA) was used for data manipulation and statistical analysis. Fisher's exact test was used to evaluate similarities between the CKC and LEEP groups. Time-to-event (survival) analysis was performed using Cox models to investigate patient and clinical factors associated with disease persistence and/or recurrence. Variables included in the modelling process were age at diagnosis, SEIFA indices, type of treatment (CKC or LEEP), margin status, and depth of excised tissue. Statistical significance was determined as a p-value < 0.05 and the 95% confidence intervals (CI) for hazard rate ratios were calculated. Plausible interaction terms were tested using likelihood ratio tests. Violation of the Cox model proportional hazard assumption was tested using Schoenfeld residuals. Due to small numbers, time to event analysis was not performed for cervical cancers.

3. Results

3.1. Study cohort

There were 338 patients with ACIS eligible for the study following exclusion of 8 patients who had a hysterectomy as initial treatment and 16 patients for whom follow-up data were not available. An overview of the study cohort is presented in Fig. 1. The mean age was 33.2 years (range 18 to 76 years) and the median follow-up interval was 3.6 years (range < 1 year to 11.8 years). Two hundred and thirty one patients (68.3%) had a CKC while the remainder (n = 107, 31.7%) had a LEEP procedure. The clinicopathological findings are summarised in Table 1.
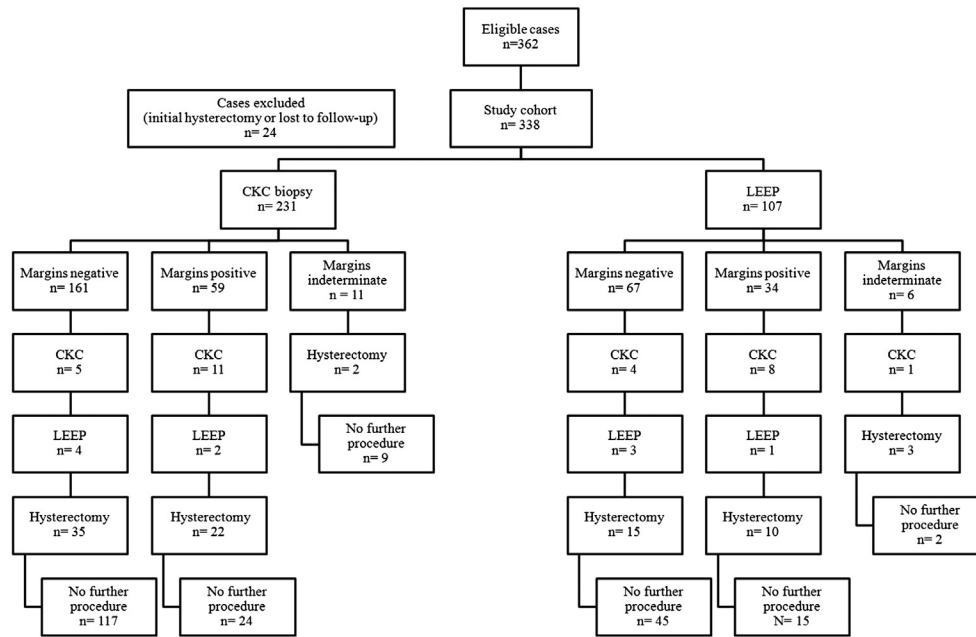
Fig 1. Overview of patient cohort and their associated health outcomes following initial treatment of ACIS.

3.2. Margin status

The biopsy margins were indeterminate in 17 cases (Fig. 1). In the remaining 321 specimens, positive margins were documented in 93

Table 1
Clinicopathological summary according to initial treatment (n = 338).

	CKC biopsy		LEEP		p-Value
	n = 231	%	n = 107	%	
Age (years)					
≤30	92	39.8	47	43.9	0.476
>30	139	60.2	60	56.1	
Socio-economic index					
Least disadvantaged	76	32.9	29	27.1	0.159
Less disadvantaged	48	20.8	17	15.9	
Middle	36	15.6	30	28.1	
More disadvantaged	49	21.2	21	19.6	
Most disadvantaged	22	9.5	10	9.3	
Initial diagnosis					
Cervical cytology	156	67.5	77	72.0	0.413
Punch biopsy	75	32.5	30	28.0	
Number of specimens					
1	209	90.5	72	67.3	0.000
>1	22	9.5	35	32.7	
Specimen depth (mm)					
Mean (range)	16.1	(2–40)	10.7	(2–27)	0.000
Specimen depth group (mm)					
≤10	58	25.1	63	58.9	0.000
>10–15	58	25.1	27	25.2	
>15–≤40	115	49.8	17	15.9	
Concurrent CIN					
Absent	92	39.8	50	46.7	0.232
Present	139	60.2	57	53.3	
Margin status					
Negative	161	69.7	67	62.6	0.432
Positive	59	25.5	34	31.8	
Indeterminate	11	4.8	6	5.6	

CKC — cold knife cone, LEEP — loop electrosurgical excision procedure.

(29%) cases including 34 LEEP biopsies (31.8%) and 59 CKC specimens (25.5%) (p = 0.432, Fig. 1 and Table 1).

3.3. Number of surgical specimens excised

LEEP was associated with a greater likelihood of more than one surgical specimen being excised during the procedure compared to CKC (see Table 1).

3.4. Follow-up period (<12 months post treatment)

In the 12 months following the initial CKC or LEEP biopsies, 105 (31%) patients underwent further histological evaluation due to an abnormal Pap smear and/or abnormality at colposcopy. Of these, 70 had negative findings, 5 had CIN 1, 24 had persistent disease (ACIS) and eight patients were diagnosed with endocervical adenocarcinoma. Of the 24 cases with persistent ACIS, 10 (41.7%) had negative pathological margins in the original treatment specimen. The remaining 233 patients underwent cytological surveillance which was either negative or showed only low-grade abnormalities within the immediate post treatment 12 month period.

3.5. Surveillance period (≥12 months post treatment)

After excluding the 86 patients who had disease persistence, adenocarcinoma, or who underwent hysterectomy in the follow-up period, 252 women entered the surveillance period. Of these, 57 (22.6%) women underwent further treatment (CKC biopsy or LEEP) and histological evaluation. Forty-four had negative findings, 7 had CIN 1, 2 had CIN 2/3, 3 had recurrent ACIS, and 1 patient had adenocarcinoma. The remaining 195 (77.4%) women had cytological surveillance showing either negative findings or low-grade abnormalities. No patient died of cervical cancer during the study period. Overall, 27 (8.0%) patients had ACIS persistence/recurrence and a further 9 (2.7%) patients were diagnosed with adenocarcinoma during the follow-up and surveillance periods.

3.6. Significance of positive margins

The initial treatment specimen in 93 patients showed positive pathological margins. Of these patients, 54 (58%) underwent a subsequent excisional procedure and the findings are presented in Table 2. The remaining 39 (42%) patients had surveillance only; none of these patients had recurrent ACIS or developed cervical adenocarcinoma.

3.7. Factors associated with disease persistence and recurrence

The results of the Cox regression analysis for disease persistence and recurrence are summarised in Table 3. Positive margin status was associated with a 3.4 (95% CI 1.5–7.8) times increased rate of ACIS persistence and/or recurrence. After adjusting for margin status there was no statistically significant association between patient age, socio-economic status, coexistence of CIN 2/3, specimen depth or treatment type (CKC biopsy or LEEP) and ACIS persistence and/or recurrence.

4. Comment

This large population-based study found no difference in ACIS disease persistence/recurrence between CKC and LEEP and no significant difference in the rate of positive margins between the two treatment modalities.

To date there have been only a small number of studies which have compared the efficacy of CKC biopsy to LEEP for the treatment of ACIS. Many are single institution reviews and are limited due to age restriction (excluding either older or younger women) and/or small sample size [5,6,11,17–19,28]. Women wishing to preserve their fertility may opt for conservative treatment following the diagnosis of ACIS, but to date there are conflicting data regarding rates of recurrence and residual disease in these patients [29–32].

To our knowledge this is the largest study of women with biopsy confirmed ACIS to have analysed outcomes according to patient age, socio-economic status, coexistence of CIN 2/3 and margin status following treatment with either LEEP or CKC biopsy. We also investigated ACIS persistence and recurrence by specimen depth because a possible explanation for our results is that LEEP may have been used to treat smaller ACIS lesions. However, there were no significant differences between LEEP and CKC in the proportion of persistent or recurrent ACIS when stratifying outcomes according to specimen depth (Table 3). It is interesting to speculate whether deep excisions (>15 mm) are required to adequately treat ACIS given that the depth of excision was

Table 2
Histology findings in patients with positive margins who underwent a second excisional procedure (n = 54).

Second procedure	Initial procedure	
	CKC biopsy n = 35	LEEP n = 19
CKC biopsy		
Negative	3	4
Low-grade changes	1	0
ACIS	6	2
Adenocarcinoma	1	2
LEEP		
Negative	1	0
Low-grade changes	0	0
ACIS	1	1
Adenocarcinoma	0	0
Hysterectomy		
Negative	14	8
Low-grade changes	0	0
ACIS	4	1
Adenocarcinoma	4	1

CKC — cold knife cone, LEEP — loop electrosurgical excision procedure.

Table 3
Hazard ratios of persistent or recurrent endocervical neoplasia according to age, socio-economic index, concurrent CIN and margin status.

Variable	Hazard rate ratio	95% confidence interval	p-Value
Age (years)			
≤30	0.7	0.3–1.8	0.477
>30 (base)	1.0		
Socio-economic index			
Least disadvantaged (base)	1.0		
Less disadvantaged	1.6	0.4–5.9	0.469
Middle	1.7	0.5–6.1	0.433
More disadvantaged	3.0	0.9–9.6	0.068
Most disadvantaged	0.6	0.1–5.8	0.689
Initial treatment			
LEEP	0.8	0.3–2.0	0.578
CKC biopsy (base)	1.0		
Number of specimens			
1 (base)	1.0		
>1	0.9	0.3–2.5	0.847
Concurrent CIN			
Absent (base)	1.0		
Present	0.9	0.4–2.2	0.870
Margin status			
Negative (base)	1.0		
Positive	3.4	1.4–7.8	0.004
Indeterminate	1.2	0.1–9.5	0.885
Specimen depth (mm)			
≤10	1.6	0.6–4.0	0.337
>10–15	0.4	0.1–1.5	0.183
>15–≤40 (base)	1.0		

CKC — cold knife cone, LEEP — loop electrosurgical excision procedure.

significantly greater in the CKC group compared to the LEEP group but there were no differences in outcomes. However, our study was not designed to assess this as the differences in depth of excision between the two groups may have reflected clinical decisions, which we were unable to verify. For example, clinicians may have opted to use LEEP for smaller ACIS lesions and CKC for larger lesions so we cannot conclude that deeper excisions are 'over-treatment' of ACIS. A carefully selected procedure will likely be the appropriate procedure for a particular patient.

LEEP was associated with a greater likelihood of more than one surgical specimen being excised compared to CKC but many of these are likely to have included intentional two-stage procedures (LEEP followed by 'top hat' endocervical sampling) as well as technically difficult procedures which resulted in multiple, fragmented or incomplete specimens. Many of the latter would, however, likely result in indeterminate margins histologically. It is noteworthy that there was no significant difference in margin status between CKC and LEEP. A single intact specimen is, of course, ideal for comprehensive histological assessment.

The management of women diagnosed with ACIS following LEEP or CKC biopsy is often dependent on the patient's age and fertility requirements and the status of the excision margins. Hysterectomy is recommended for women who have completed child bearing [6,11–13,33] because cytological follow-up is less reliable and rates of recurrence may be high [5,12,17,19,32]. It is also noteworthy that 10/24 patients in this series who had ACIS on a second excisional procedure had negative initial biopsy margins. This may reflect the multifocal distribution of ACIS in some cases and emphasizes the requirement for follow-up even after apparently complete local excision.

The main limitation of this study is its retrospective design so it is conceivable that selection bias or exposure to confounding variables may have influenced outcomes between the two treatment groups. Although this is the largest population-based study ever reported, it was only sufficiently powered to detect a relatively large difference in

the treatment effects due to the small number of recurrent ACIS cases. The median follow-up interval was only 3.6 years and it is our intention to continue to follow this patient cohort. Strengths of the study are its large population-based cohort and data linkage.

Potential sequelae of CKC and LEEP include adverse obstetric outcomes such as second trimester miscarriage and pre-term delivery [14,20,22,23,34]. Epidemiological data suggest that these risks correlate with depth of excision and are more frequent following CKC [22,23]. This study demonstrates that women who were managed conservatively following the diagnosis of ACIS had equivalent rates of positive margins and oncologic outcomes whether they were treated by LEEP or CKC. Given that CKC may be associated with an increased risk of adverse obstetric outcomes compared to LEEP, and that rates of ACIS persistence/recurrence are comparable for both treatment modalities, LEEP may be the preferred treatment option in patients in whom fertility preservation is important. The only significant determinant of disease persistence or recurrence was the presence of a positive histo-pathological margin, which is in accordance with findings from previous studies [6,9,35–39].

In conclusion, LEEP may be an appropriate treatment option for women with ACIS who wish to preserve fertility since this does not appear to compromise oncologic outcomes when compared to CKC. However, further prospective studies are needed to confirm these findings.

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Chapter 4:

Spontaneous regression of CIN2: Investigation of incidence in women aged <25 years

Research output

Published manuscripts

1. **Munro A,** Powell R, Cohen P, Bowen S, Spilsbury K, Codde J, Semmens J, O'Leary P, Williams V, Leung Y. *Evidence for spontaneous regression of cervical intraepithelial neoplasia-grade 2 in young Western Australian women: A review of 2,692 cases.* Accepted 21 November 2015 by Acta Obstetricia et Gynecologica Scandinavica (manuscript number: AOGS-15-0599.R1).

Conference presentations

1. Powell R, **Munro A**, Bowen S, O'Leary P, Semmens JB, Codde J, Williams V, Spilsbury K, Steel N, Leung Y. **CIN2 regression for young patients who were conservatively managed.** *15th Biennial Meeting of the International Gynecologic Cancer Society* Melbourne, Australia. November 2014 (poster).
2. Powell R, **Munro A**, Bowen S, O'Leary P, Semmens JB, Codde J, Williams V, Spilsbury K, Steel N, Leung Y. **CIN2 regression for young patients who were conservatively managed.** 2014 *World Cancer Congress.* Melbourne, Australia. November 2014 (poster).

4.1 Background

The acquisition of knowledge has occurred much more rapidly for the epidemiological and biological features of HSIL than for glandular lesions (AEC and/or ACIS). Consequently, in 2001, evidence-based management guidelines were implemented in Australia for women aged < 25 years with histologically confirmed HSILs[7].

It is well accepted that the persistent infection of the cervix with high-risk or oncogenic HPV (HR HPV) is a prerequisite for the development of CIN and cervical cancer[88]. A histological diagnosis of CIN1 is linked with benign viral replication that regresses in most cases[89]. Previous studies involving adult women report CIN1 regression rates of 70–80%, whereas spontaneous regression has been reported up to 90% in adolescent and young women[82-92]. Because of the high regression rate, it is recommended in Australia and the USA that clinicians conservatively manage adolescents with CIN1 with observation rather than administering treatment[3, 7].

However, the biological behaviour and treatment of CIN2 remains controversial for many clinicians. Few studies have investigated CIN2 regression rates for young women (<25 years) while preliminary analyses report that up to 65% of CIN2 cases naturally regress for this population of women[27, 64, 65]. Although it has been widely accepted that conservative management for adolescents with CIN2 is reasonable, there is limited data examining the issue in women aged 20 to 25 years. Given the potential for adverse health complications after treatment, a large proportion of practitioners offers women in this age group conservative management for CIN2[27, 93, 94]. The 2005 NHMRC Guidelines currently do not have specific management recommendations for young women aged <25 years with biopsy confirmed CIN2. Given the diversity of management practices and the lack of evidence on patient outcomes on a global scale, there is an urgent need to determine if surveillance could be an appropriate option for this young cohort of women.

Therefore, Chapter 4 (Objective 3) provides important findings that could be used to help clinicians avoid excisional or ablative treatment (LEEP/CKC biopsy) for selected patients who have received appropriate counselling and who are able to comply with the more intensive and prolonged follow-up required in a conservative management approach (Publication 3).

4.2 Aim

This study aimed to investigate health outcomes in conservatively managed young women with CIN2.

4.3 Methods

A retrospective study of women aged 18 to 24 years diagnosed with CIN2 on cervical biopsy between 01 January 2001 to 31 December 2012. Women who remained untreated at ≥4 months were allocated to a "conservative management" group.

Cervical cytology and/or biopsy test results were used to report lesion regression (defined as the absence of dysplasia or an epithelial lesion of lower grade than CIN2) and disease persistence (defined as CIN2, CIN3 or adenocarcinoma in situ).

4.4 Results

There were 924 (38.2%) women with CIN2 who were 'conservatively' managed. There were 152 (16.4%) women who had a lesion more severe than CIN2 detected within 24 months of initial diagnosis, of which 144 were CIN3 and 8 were ACIS.

Overall, there was no statistically significant association identified between rates of regression and the patient's age, Socio-Economic Indexes for Areas or Accessibility/Remoteness Index of Australia indices. The two-year CIN2 regression rate was estimated to be 59.5% (95% CI 0.5 - 0.6) in this cohort of young women.

4.5 Conclusion

In conservatively managed young women with CIN2 there was a high rate of spontaneous disease regression. Thus, excisional or ablative treatments may be avoided in selected patients who received appropriate counselling and who are able to comply with the more intensive and prolonged follow-up required in conservative management of CIN2.

4.6 Published Manuscript

Munro A, Powell R, Cohen P, Bowen S, Spilsbury K, Codde J, Semmens J, O'Leary P, Williams V, Leung Y. **Spontaneous regression of CIN2 in women aged 18-24 years: a retrospective study of a state-wide population in Western Australia.** Accepted 21 November 2015 by *Acta Obstetricia et Gynecologica Scandinavica* (manuscript number: AOGS-15-0599.R1).

AOGS ORIGINAL RESEARCH ARTICLE

Spontaneous regression of CIN2 in women aged 18–24 years: a retrospective study of a state-wide population in Western Australia

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Abstract

Introduction. CIN2 has a high rate of spontaneous regression in young women and may be managed conservatively in appropriately selected patients. This study aimed to investigate health outcomes in women aged 18–24 years with biopsy-confirmed CIN2. *Material and methods.* A retrospective cohort study of Western Australian women aged 18–24 years diagnosed with CIN2 on cervical biopsy from 1 January 2001 to 31 December 2010. Women who had not received treatment at ≥4 months following CIN2 diagnosis were classified as managed 'conservatively'. Subsequent cervical cytology and/or biopsy test results were used to report lesion regression (absence of dysplasia or an epithelial lesion of lower grade than CIN2) and disease persistence (CIN2, CIN3 or ACIS). *Results.* Follow-up data were available for 2417 women of whom 924 (38.2%) were 'conservatively' managed. In all, 152 (16.4%) conservatively managed women had a lesion more severe than CIN2 detected within 24 months of initial diagnosis, of which 144 were CIN3 and eight were ACIS. There was no statistically significant association between rates of regression and patient age, Socio-economic Indexes for Areas or Accessibility/ Remoteness Index of Australia indices. The 2-year regression rate for CIN2 was estimated to be 59.5% (95%CI 0.5–0.6) in this cohort of women. *Conclusion.* In conservatively managed young women with CIN2 there was a high rate of spontaneous disease regression. Thus, excisional or ablative treatments may be avoided in selected patients who receive appropriate counseling and who are able to comply with more intensive and prolonged follow-up requirements.

Abbreviations: ACIS, adenocarcinoma-in-situ; CIN, cervical intraepithelial neoplasia (grade 2/3); HSIL, high-grade squamous intraepithelial lesion; LEEP, loop electrosurgical excisional procedure; LSIL, low-grade squamous intraepithelial lesion; WA, Western Australia.

Introduction

High-grade cervical intraepithelial neoplasia (CIN) is a precursor to cervical squamous cell carcinoma (1–3). The peak incidence of high-grade CIN is in women under the age of 25 years but cervical squamous cell carcinoma is rare in this age group (4–7). There are data to show that a significant proportion of cases of CIN2 in adolescent and young women (under the age of 21 years) will spontaneously regress (7–9) and because the risk of progression to malignancy appears to be low in this age group, excisional or ablative treatment may not be indicated. Young women diagnosed with CIN2 who are likely to comply with follow up may be offered conservative management including observation with colposcopy and cytological evaluation every 4–6 months to permit spontaneous regression of CIN2 and to avoid potentially unnecessary and costly treatment (7–12). Excisional treatments such as the loop electrosurgical excisional procedure (LEEP) are associated with physical, psychological (13–15) and obstetric morbidity (16–18) and may have a negative impact on sexual function (14,19,20).

Guidelines suggest that conservative management for adolescents with CIN2 may be considered in appropriately selected cases, but few studies have addressed this issue in women aged 20–25 years (7,10). Given the potential for treatment-related complications, many practitioners have offered women in this age group who are diagnosed with CIN2 the option of conservative management. The aim of our study was to investigate the rate of spontaneous regression of CIN2 in Western Australian women aged 18–24 years to determine whether conservative management for appropriately selected patients in this age group may be a reasonable alternative to immediate treatment.

Material and methods

This study was a retrospective cohort study. Women aged 18–24 years were followed-up from the time of their first CIN2 diagnosis (cervical biopsy test result) until their last cytology/histology record. Ethical approval for this study was granted by the Human Research Ethics Committees of Curtin University (ethics research project number: HR 86/2012) and the Western Australian Department of Health Human Research Ethics Committee (ethics research project number: 2012/49).

The Western Australian Data Linkage System provided a de-identified extraction of linked data for the period 1 January 2001 to 31 December 2010 from the Cervical Screening Register of Western Australia (WA) and the Hospital Morbidity Data System (HMDS). The Western Australian Data Linkage System is an internationally renowned, population-based, validated and ongoing data linkage system that creates links among a number of state health administrative datasets (21–23).

The National Cervical Screening Program encourages eligible women (women that have not had a hysterectomy and have commenced sexual activity) aged 18–69 years to have a cervical smear every 2 years. As part of the National Cervical Screening Program, the WA Cervical Cancer Prevention Program maintains and operates the Cervical Screening Registry of WA. The Cervical Screening Registry of WA is a voluntary "opt-off" confidential register which compiles all cervical test results [cervical smear, cervical biopsy and Human Papillomavirus (HPV) tests] that cytopathology laboratories are legislatively required to report. A de-identified dataset was extracted from the CSR of WA that contained cervical screening histories for all women under the age of 25 years who resided within WA at the time of their CIN2 diagnosis. Cervical Screening Registry follow-up data were available until May 2013.

Women were allocated measures of socioeconomic status using the Socio-economic Indexes for Areas for Australia obtained through the Australian Bureau of Statistics (24). Additionally, women's postcodes were assigned to one of four Accessibility/Remoteness Index of Australia categories (25). Due to small numbers, remote and very remote postcodes were collapsed into one category for the purposes of this study.

The Hospital Morbidity Data System records discharge summaries from all Western Australian hospitals (private and public and day surgery clinics). For women who did not have a biopsy treatment record, the International Classification of Disease code N87.1 for moderate cervical dysplasia and associated procedural codes were used to identify women who had ablative and excisional techniques performed. Procedural codes included excision (cone biopsy by cold knife or laser) and ablation (radical diathermy of cervix, large loop excision transformation zone, laser ablation of cervix and other ablative procedures of the cervix).

Cervical cytology test results were classified according to the Australian Modified Bethesda System 2004. This classification system is comparable internationally and

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Key message

Conservatively managed young women with CIN2 had a 59.5% spontaneous regression rate. Conservative management is an option for selected patients who receive appropriate counseling and who are able to comply with follow up.

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reflects the increased understanding of HPV biology and the development of cervical cancer. In the present study we refer to findings from cervical cytology as high-grade squamous intraepithelial lesion (HSIL) or low-grade squamous intraepithelial lesion (LSIL). Histological findings are referred to as CIN2 and CIN3.

Only women aged 18–24 years with a histological confirmation of CIN2 were included in this study. Women were excluded if they (1) had a past history of a histologically confirmed high-grade intraepithelial lesion that was more severe than a CIN2, or (2) 12 months of follow-up data (cervical cytology or histology) were unavailable.

The Australian Guidelines recommend that women with a cervical smear test result of HSIL should be referred to a gynecologist for colposcopic assessment and targeted biopsy[4]. Ideally women with cervical cytology showing HSIL or possible HSIL should be assessed within 2 months of diagnosis. Assessment includes colposcopy +/− cervical biopsy. As such, women were allocated into a group dependent on when CIN2 treatment (excisional or ablative) was performed. To allow for women's attendance for gynecological assessment and treatment, time-frames were slightly extended to the following:

(1). If the woman was treated for CIN2 within 4 months she was allocated to the "immediate treatment" group (4).

(2). If treatment for CIN2 was performed after more than 4 months women were allocated to the "conservative management" group (4,7).

Outcome measures were disease regression (i.e. negative or low-grade lesions including an LSIL on cytology and/or mild dysplasia (CIN1) or atypia on a subsequent biopsy), disease persistence including HSIL (CIN2, CIN3 or adenocarcinoma-in-situ) and disease progression (cervical cancer). Disease regression, persistence or progression were determined from histology test results where possible.

In the absence of histology, cytological findings were used and a hierarchical system was adopted to report the most severe diagnosis for the patient. In the event that a patient had evidence of regression but at a later follow-up visit cytology or histology confirmed persistence or disease progression, the latter diagnosis was reported.

Statistical analysis

Equality of demographic and clinical characteristics of women on different treatment pathways was tested using the chi-squared test. Time-to-event analyses were performed to investigate factors associated with the rate of regression for women who remained untreated ($n = 924$) for CIN2 by 24 months. The follow-up interval was recorded as the time from the CIN2 diagnosis to disease regression (the event) defined as negative cytology and/or biopsy, LSIL or a low-grade glandular abnormality. Participant follow up was censored at treatment of CIN2 disease, progression or at the time of the last available cervical cytology and/or biopsy result. If women underwent treatment but had a negative treatment specimen on histopathology they were recorded as having had disease regression. Covariates included in the time-to-event analysis were age, socio-economic status and an index of accessibility to services.

Statistical significance was determined as a p-value <0.05. STATA Version13.0 (Stata Corporation, College Station, TX, USA) was used for data manipulation and statistical analysis.

Results

During the 10-year study period, 2692 women were aged 18–24 years at the time of their initial CIN2 diagnosis. Of these, 275 women were excluded from the study because 12 months of follow-up data (cytology or histology test results) were unavailable ($n = 275$). For the remaining 2417 women, demographic information and comparative statistics are reported in Table 1. Conservative management was more likely, the younger the age of the woman and in those living in urban areas. Management approach did not vary by socio-economic status. A total of 38% of women had an HSIL (CIN2/3) detected on their referral cytology test result within 24 months prior to their CIN2 diagnosis.

There were 1493 (61.8%) women who underwent treatment within 4 months of diagnosis (immediate treatment group). The mean time from initial diagnosis to treatment was 1.5 months in this group. Of the 1493 women immediately treated, 58 (3.9%) women underwent laser ablation of the cervix and no histological specimen was available. Of these women, 56 had negative follow-up cytology and/or histology findings and two women were confirmed to have disease persistence. The remaining 1435 women were treated by either LEEP or cold knife cone biopsy. The majority of women immediately treated had CIN2 (62.5%) in their surgical specimen findings (Table 2) and a smaller proportion of women either had either negative histopathology or a low-grade cervical abnormality (17.3%).

There were 924 (38.2%) women managed 'conservatively'. During the 24-month follow-up period, 25 women subsequently underwent laser ablation and their follow-up cytology test results were negative ($n = 17$), LSIL ($n = 5$), possible and persistent HSIL ($n \leq 5$). In all, 437 women who were initially managed conservatively subsequently underwent treatment within the 24-month fol-

Table 1. Women's baseline demographic information by management category

	Immediate treatment group (*n* = 1493)	Percentage (%)	Conservative treatment group (*n* = 924)	Percentage (%)	Chi-squared *p*-value
Women's age (years)					
18–19	208	13.9	176	19.1	0.003
20–21	464	31.1	281	30.4	
22–24	821	55.0	467	50.5	
Women's referral cytology test result (within 24 months of biopsy confirmed CIN2 diagnosis)					
Negative	7	0.5	4	0.4	0.000
Low-grade squamous intraepithelial lesion (CIN 1)	19	1.2	61	6.6	
Possible high-grade squamous intraepithelial lesion (HSIL)	6	0.4	20	2.2	
HSIL (CIN2/3)	567	38.0	439	47.5	
No referral cytology test result present	894	59.9	400	43.3	
Accessibility/Remoteness Index of Australia					
Major city	995	66.6	690	74.7	0.002
Inner regional	235	15.7	109	11.8	
Outer regional	128	8.6	60	6.5	
Remote/very remote	117	7.9	58	6.3	
Unknown (Post Office Box)	18	1.2	7	0.7	
Socio-economic Indexes for Areas for Australia					
Least disadvantaged	467	31.3	323	35.0	0.315
Less disadvantage	243	16.3	155	16.8	
Middle	334	22.4	181	19.6	
More disadvantaged	266	17.8	165	17.8	
Most disadvantaged	165	11.0	93	10.1	
Unknown (Post Office Box)	18	1.2	7	0.7	

CIN, cervical intraepithelial neoplasia; HSIL, high-grade squamous intraepithelial lesion.

low-up period with either LEEP (*n* = 402) or cervical cold knife cone biopsy (*n* = 35). Their histopathology findings are reported in Table 2. Most were CIN2 (22.9%), although a proportion of women (15.6%) had CIN3 confirmed in their treatment specimen. Of the 152 (16.4%) women who had a lesion more severe than CIN2 detected within 24 months of their initial CIN2 diagnosis, 144 were CIN3 and eight were ACIS.

There were 462 women with a histological diagnosis of CIN2 (on cervical punch biopsy) who did not undergo treatment during the follow-up period. The majority (*n* = 404) of these women had repeat cervical cytology within 6 months of initial diagnosis. A small proportion (3.7%) subsequently had cervical cytology reported as CIN3 during the study follow-up period but are yet to have histological confirmation (outside the study period). In 445 women, follow-up cervical cytology and histology indicated disease regression. The median follow-up time for women without a treatment record was 1.8 years.

Multivariate time to event analysis was performed for those women (*n* = 924) conservatively managed to obtain the disease regression hazard rate ratio. Women were censored after treatment and/or when disease progression

was confirmed. There was no statistically significant association identified between the rate of regression and patient age (potentially due to age intervals being very narrow, hazard ratio (HR) 1.2, 95% CI 1.0–1.5), Socio-economic Indexes for Areas for Australia (HR 1.1, 95% CI 1.0–1.2) or Accessibility/Remoteness Index of Australia indices (HR 1.0, 95% CI 0.8–1.1).

A Kaplan–Meier graph (Figure 1) was constructed (censoring women at the time of treatment and/or if disease progression was identified) which highlights that the majority of women within the "conservative management" group regressed within 12 months following their initial CIN2 diagnosis. The 2-year CIN2 regression rate was estimated to be 59.5% (95% CI 0.5–0.6) in this cohort of young women.

Discussion

The aim of our study was to investigate disease outcomes of conservatively managed women aged 18–24 years with biopsy-confirmed CIN2. Outcome variables measured included rates of CIN2 regression, persistence or progression to higher grade dysplasia or invasive cervical

Table 2. Treatment performed and final histologic condition at time of treatment by management category (within 12 months of CIN2 diagnosis)

	Immediate treatment group (*n* = 1493)	Percentage (%)	Conservative treatment group (*n* = 924)	Percentage (%)
Treatment performed				
Laser destruction	58	3.9	25	2.7
Cold knife cone biopsy	138	9.2	35	3.8
LEEP	1,297	86.9	402	43.5
No treatment record present (within 24 months of CIN2 diagnosis)*	0	0	462	50.0
Treatment outcome				
Negative	82	5.5	24	2.6
Low-grade intraepithelial abnormality	176	11.8	49	5.3
CIN2	933	62.5	212	22.9
CIN3	231	15.5	144	15.6
Adenocarcinoma-in-situ	11	0.7	8	0.9
Squamous cell carcinoma	<5**	–	0	0.0
Adenocarcinoma	<5**	–	0	0.0
No treatment outcome available	58	3.9	487	52.7

CIN, cervical intraepithelial neoplasia; LEEP, loop electrosurgical excisional procedure.
*No histologic condition was reported because cervical cytology test results were used to determine the outcome in the conservative treatment group, or the treatment was ablation and no histologic condition was available.
**Due to small case numbers, <5 has been reported to ensure women's confidentiality.
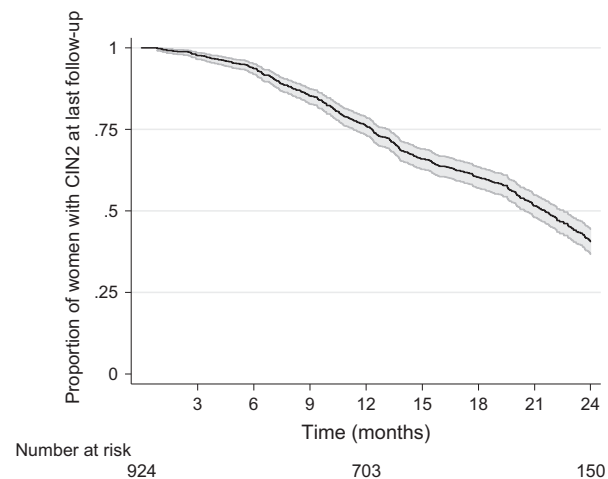

Figure 1. Kaplan Meir Curve showing the proportion of women who underwent conservative treatment (n = 924) who remained with CIN2 within 24 months of initial diagnosis. Women were censored at time of treatment or when disease progression was identified as they could not contribute further time at risk of regression.

cancer or other associated gynecological disease. Linked administrative health datasets were used to ascertain these outcomes in a large cohort of Western Australian women with biopsy-confirmed CIN2. From Kaplan–Meier analysis it was estimated that 59.5% of conservatively managed women with CIN2 regressed by 24 months post diagno-sis. There were no cases of invasive cervical cancer among the conservatively managed cohort. Furthermore, 331 (13.7%) patients who received immediate or conservative treatment were found to have either normal or low-grade histology in the excisional specimen.

The management of young women (<25 years) with screen-detected cervical abnormalities is contentious as there is no clear evidence to suggest that screening patients under this age prevents cervical cancer (26–28). Thus, previous management strategies are no longer universally accepted for young women with biopsy-con-firmed CIN2 (7,9,11). As such, specialist obstetrician/gy-necologists are encouraged to consider offering conservative management to appropriately selected patients, in order to minimize potential treatment-related physical, psychological and obstetric morbidity (7).

There is evidence demonstrating CIN2 regression in up to 65% of adolescents and young women (<21 years) over an 18-month period and hence conservative man-agement in this population may be warranted (8,9,12). However, only a small number of studies have investi-gated the rate of CIN2 regression in women up to 25 years of age, most of which are limited due to their small sample size (7). To our knowledge this is the largest population-based study to have analysed outcomes by patient age and socio-economic status in women aged 18–24 years with biopsy-confirmed CIN2. This study

contributes to and reinforces the health outcomes highlighted in previous research (7).

In any study of natural history outcomes in untreated CIN2, an important consideration is misclassification of histopathological diagnosis. The reporting of cervical specimens (cytology and biopsy specimens) possesses a degree of subjectivity and CIN2 may be over-diagnosed in some cases. In Australia, laboratories that report cervical abnormalities are required to comply with mandatory annual Performance Measures (29) and are subject to independent verification of data submitted by the laboratory to the Royal College of Pathologists Australasia Cytopathology Quality Assurance Program. These measures have enhanced external quality assurance procedures in Australia (29).

Limitations of our study include its retrospective design and the error inherent in all databases. For example, excisional procedures may have been performed on an outpatient basis and not captured in hospital records. However, the mandatory reporting of the histological findings of cervical specimens to the Registry ensures data completeness is obtained. The quality assurance processes employed ensure the level of error within the register is acceptable. A further limitation of our study is the lack of information regarding colposcopy findings, and therefore no information on other factors, which may have influenced whether women were treated immediately or not. This could introduce bias in the results. The reasons women had treatment performed were not clearly identified and consequently treatment intervals varied. Additionally, disease regression could not always be confirmed histologically.

Furthermore, our inclusion criteria to this study required biopsy confirmation of a CIN2 lesion. As such, the lesion may not have "truly" spontaneously cleared, as the biopsy may have accelerated the clearance of the disease (i.e. specifically if it was a very small lesion). It is important to note that CIN2 is the least reproducible of all cervical diagnoses, and it is possible that the "regression" of CIN2 is dependent on the individual pathologist reporting the lesion (30–33). The potential inclusion of "equivocal" CIN2 lesions could also be expected to increase the overall regression rate and, consequently, regression may have been over-reported (30,31). These limitations emphasize the need for further prospective studies that report treatment determinants and also reproducible biomarkers (i.e. p16 staining of CIN2 specimens).

In recommending conservative management following the diagnosis of CIN2, patient safety is paramount. In our study among those patients who were treated conservatively, none progressed to invasive cervical cancer, although eight cases of adenocarcinoma-in-situ (ACIS) were identified (0.9%). Among those women who received immediate treatment, there were cases of ACIS ($n = 11$),

squamous cell carcinoma ($n \leq 5$) and adenocarcinoma ($n \leq 5$) that had not been identified initially. These cases highlight the need for cautious implementation of a conservative management protocol in young women diagnosed with CIN2, and the need for careful selection of patients, regular follow-up evaluation, maintenance of clinical standards and appropriate follow-up systems.

Potential sequelae of conization and LEEP include not only the physical and psychological but also adverse obstetric outcomes such as second trimester miscarriage and early pre-term delivery (34–37). Epidemiological data suggest that these risks correlate with depth of excision and are more frequent following conization (34,37). Based on the 59.5% regression rate reported in this study, conservative treatment of CIN2 may be an appropriate option, in the form of regular surveillance, for patients less than 25 years of age. These women should remain under specialist care, which routinely provides colposcopy, cytological testing and quality assurance throughout the patient's clinical management for at least 24 months prior to invasive treatment.

Acknowledgments

Funding

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Chapter 5:

Investigation of follow-up of women treated for high-grade squamous intraepithelial lesions

5.1 Background

Although the follow-up of women with biopsy confirmed ACIS is not widely reported, a new management pathway was outlined for women treated for HSILs in 2005[7]. Prior to 2005, the Australian guidelines for follow-up after treatment for HSILs recommended ongoing annual cytological testing. An alternative strategy is to use DNA testing for HPV (in conjunction with conventional cytology) as a ToC[7]. This screening policy change significantly alters the screening pathway for women treated for HSILs as it brings women back to routine screening earlier, thereby reducing the amount of post-treatment surveillance required.

The ToC was introduced into the 2005 NHMRC Guidelines as the link between HR HPV infection and the development of cervical cancer is well recognised, with almost 99.7% of cervical cancers associated with a type of HR HPV[8]. It is also known that women who have been treated for an HSIL and test negative for HR HPV infection are at a low risk of developing cervical cancer in the short to medium term.

Although this management pathway is clearly beneficial to women that have been treated for an HSIL and despite its national implementation in Australia since 2005, there has been little national evaluation of practitioner's awareness/knowledge of and their compliance with the ToC management pathway[48, 94, 95]. The NCSP found that WA was well equipped to utilise jurisdictional CSR data and the WADLS link to other administrative datasets (see Chapter 2) to determine whether women with biopsy confirmed CIN2/3 were treated. By accessing linked data, WA has been able to provide an overall ToC compliance rate to the NCSP that could in turn use this evidence to support the future development of educational policies to promote this critical follow-up protocol among GPs who are at the fore in terms of the ToC for eligible women.

5.2 Aim

To conduct a population-based study investigating practitioners' knowledge of and compliance with ToC.

5.3 Methods

5.3.1 Investigation into GPs knowledge and awareness of ToC through dissemination of a questionnaire

After consultation with key stakeholders, an anonymous, self-completion questionnaire was developed and disseminated to GPs who had provided cervical cytology. Effectively engaging GPs to participate in research initiatives is challenging because of their high workload and limited availability of time to complete surveys. To facilitate the participation of GPs in this initiative, a survey (see Appendix 6) requiring a maximum of five minutes for completion was designed. The survey was piloted with five GPs to determine whether the survey questions were clinically appropriate, clear, and sequenced logically. The feedback from this pilot was used to restructure the survey questions and ensure ease of collection.

The WACCPP utilised the CSR of WA to identify all GPs that had provided cervical screening in the prior 12-month period (1 July 2012 to 30 June 2013). Once specific GPs were identified (approximately 2,500 GPs), a manual review of the GPs demographic information was performed to confirm their latest practice address. Using the pilot feedback received, a short survey (25 questions) was developed in a tick-box format and included a final comments section for those GPs who wished to provide further comments/information. The survey format was ideal for GPs to complete between seeing different patients.

The CSR of WA disseminated the survey and invitation letter as GPs routinely receive follow-up letters from this service. To further encourage participation in this activity, a well-recognised women's health specialist, Professor Yee Leung (Gynaecologist-Oncologist at King Edward Memorial Hospital), signed the invitation letter calling the GPs to complete the enclosed survey.

5.3.2 Investigation into GPs compliance with the ToC

Women treated for an HSIL between the five-year period 01 Jan 2006 to 31 Dec 2010 were identified and followed up for at least a 27-month period. Proportions and relative odds were determined for women entering and completing the ToC management pathway within recommended time frames.

5.4 Results

5.4.1 GP questionnaire results

Responses were received from 745 GPs (30.9% response rate). A significant number (34.3%) of GPs were unaware of the use of co-testing (HPV DNA testing and cervical cytology) for the management of patients after HSIL treatment.

5.4.2 GP compliance rate with ToC

There were 5,194 women identified as 'eligible' to enter the ToC management pathway. Of these, 1,916 (37%) were managed with annual Pap smears and never had a HR HPV test performed.

There were 1,296 (25%) women who entered the ToC management pathway within the recommended time frames.

5.5 Conclusion

Overall, a significant number of Australian women did not enter (~37%) and complete (~50%) the ToC management pathway (Publication 4).

The challenge remains to advocate the ToC to practitioners to ensure women are returned to the population-screening interval in a timely manner. GPs require further support and education to ensure successful adoption of co-testing (HPV DNA testing and cervical cytology), specifically, for patients treated for an HSIL (Publication 5).

5.6 Published Manuscripts

Munro A, Codde J, Semmens J, Leung Y, Spilsbury K, Williams V, Steel N, Cohen P, Pavicic H, Westoby V, O'Leary P. **Utilisation of co-testing (human papillomavirus DNA testing and cervical cytology) after treatment of CIN: A survey of GP's awareness and knowledge**. *AFP* 2015; 44(1): 64-68.

Utilisation of co-testing (human papillomavirus DNA testing and cervical cytology) after treatment of CIN: a survey of GPs' awareness and knowledge

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Background

Patients have an increased risk of persistent/recurrent cervical disease if they received treatment for a high-grade squamous intraepithelial lesion (HSIL). Consequently, understanding whether co-testing (human papillomavirus [HPV] DNA testing and cervical cytology) is fully utilised by general practitioners (GPs) is paramount.

Methods

After consultation with key stakeholders, an anonymous, self-completion questionnaire was developed and disseminated to GPs who had provided cervical cytology.

Results

Responses were received from 745 GPs (30.9% response rate). A significant number (34.3%) of GPs were unaware of the use of co-testing (HPV DNA testing and cervical cytology) for the management of patients after HSIL treatment. Additionally, the majority of GPs reported they did not 'always' receive a clear follow-up plan for patients after treatment of an HSIL.

Discussion

GPs require further support and education to ensure successful adoption of co-testing (HPV DNA testing and cervical cytology), specifically, for patients treated for an HSIL.

Keywords

cervical intraepithelial neoplasia; human papillomavirus DNA tests; Papanicolaou test; general practice

Conventional cervical cytology is the standard screening test for identifying women who are at increased risk of cervical cancer by detecting premalignant cervical lesions.[1–3] Worldwide, countries that have adopted an organised approach to cervical screening have been successful in detecting and treating high-grade squamous intraepithelial lesions (HSIL) before possible progression to cervical cancer.[1–3] HSIL refers to moderate-to-severe changes in the cells of the cervix known as cervical intraepithelial neoplasia (CIN) 2 or CIN 3.[4] A study conducted recently reported the positive predictive value of biopsy confirmed precancerous cervical lesions to be as high as 71% for patients with an HSIL cervical cytology test result.[5] Consequently, a patient with an HSIL result should be referred as soon as practicable for colposcopic assessment and targeted biopsy.[4]

Acceptable treatment options for patients with an HSIL cytology test result that was confirmed with colposcopy and biopsy include ablative or excisional modalities.[4] However, if colposcopy is unsatisfactory or if the HSIL persists, a diagnostic excision is recommended.[4] The majority of patients will clear human papillomavirus (HPV) infection within 24 months post-treatment; however, previous studies have shown that patients with a history of treated CIN 2 and/or CIN 3 are at increased risk of recurrent high-grade disease and cervical cancer.[6] Persistent disease (≥6 months post-treatment) is often associated with endocervical gland involvement[7] and continuing HPV infection[8,9] (specifically high-risk HPV[16]). Our improved understanding that oncogenic HPV infection is instrumental in the development of cervical cancer has led to the development and utilisation of tests that can detect HPV DNA oncogenic types.[5,6,10–12]

HPV DNA testing may be implemented as an auxiliary tool, in combination with cervical cytology, to improve the management of patients at risk of further cervical disease.[4,12–14] This screening protocol takes advantage of the high sensitivity of HPV DNA tests and also the specificity of cervical cytology.[12] In 2005, best practice guidelines, known as the 'Test of Cure', were implemented in Australia. These guidelines recommend that patients should have a colposcopy and cervical cytology test 4–6 months after treatment for an HSIL.[4] If these two tests (using the two modalities) are negative, then the patient is able to return to the care of the GP and should be managed as follows:

- Cervical cytology accompanied by high-risk HPV DNA testing should commence 12 months after treatment and continue annually until the patient has tested negative for both tests on two consecutive occasions.[4]
- When the above four tests (using two modalities) are negative, the patient is encouraged to return to a regular screening regimen as appropriate for the general female population.[4]

Table 1. Characteristics of survey respondents		
	Survey respondents	
Characteristics	**n = 745**	**Percentage (%)**
Sex		
Female	431	57.9
Male	311	41.8
Not reported	3	0.4
Age (years)		
<35	64	8.6
35–44	188	25.2
45–54	239	32.1
≥55	252	33.8
Not reported	2	0.3
Years practicing as a GP		
<2	41	5.5
2–5	70	9.4
6–10	81	10.9
11–19	172	23.1
≥20	379	50.9
Not reported	2	0.3
Direct patient contact hours per week		
<10	32	4.6
11–20	133	17.9
21–40	397	53.3
41–60	164	22.0
>60	14	1.9
Not reported	5	0.7
Index of relative social disadvantage		
Most disadvantaged	48	6.4
More disadvantaged	94	12.6
Middle	94	12.6
Less disadvantaged	162	21.7
Least disadvantaged	265	35.2
Not reported	85	11.4
Accessibility/Remoteness Index of Australia		
Major city	361	48.5
Inner regional	186	25.0
Outer regional	62	8.3
Remote/Very remote	51	6.9
Not reported	85	11.4

To date, no studies have addressed compliance with the Test of Cure. Recently, Dr Heley, a senior liaison physician with the Victorian Cytology Service raised a concern that health practitioners in Australia were failing to perform HPV tests on eligible women.[15] Understanding whether this pathway has been fully utilised by GPs is important given the risk of persistent/recurrent cervical disease for patients treated for an HSIL.[6,15] Consequently, the aims of this study were to investigate GPs' awareness of and compliance with performing co-testing (high-risk HPV DNA and cervical cytology) on eligible patients (as per Australian guidelines) and the perception of support from specialist obstetrician/gynecologists (ob/gyns) in providing clear care plans that promote this management pathway for patients after treatment of an HSIL.

Methods

Participants

The Cervical Cytology Registry (CCR) of Western Australia identified all GPs who had provided a cervical cytology test in the period 1 July 2012 to 30 June 2013. Data cleansing (contacting the GP practice and reviewing the Medicare Australia list of provider contact details) was undertaken for all individual GPs to ensure the Registry had up-to-date demographic details.

Measures

The survey design included a combination of questions with categorical and Likert scale response options and, where applicable, space for participants to provide additional comments. Information was collected about the GP respondents (age, number of direct patient contact hours, number of years practicing as a GP) and questions were focused on current practices regarding management of patients who had been treated for an HSIL.

Procedure

Following approval by the Curtin University Ethics Committee (Reference number HR 86/2012), the survey was mailed to GPs, together with a covering letter and reply paid envelope. To encourage GP participation in this study, and to ensure confidentiality, the survey respondents were de-identified.

Statistical analysis

Anonymous postal survey responses were manually entered into a specific Survey Monkey collation spreadsheet and then exported into STATA/IC 13.0 (STATA Corporation, College Station, USA) for statistical analysis. GPs' age (at the time of the survey) was classified into <35, 35–44, 45–54, ≥55 years age groups. Practice postcode was used to assign the practice location into quintiles of Index of Relative Social Disadvantage (ABS 2011) and into one of three Accessibility/Remoteness Index of Australia (ARIA) levels. Logistic regression analysis was used to investigate GP factors associated with the odds of having Test of Cure knowledge and involved purposeful selection of covariates at the 5% significance level.

Results

According to the CCR of Western Australia, 2545 GPs had performed a cervical cytology test in the 12-month period from 1 July 2012 to 30 June 2013. Of these 2545 GPs, to whom surveys were posted, responses were received from 745 (29.3%) GPs. After removing the 136 (5.4%) surveys that were returned as 'undeliverable' or 'blank', this corresponded to an adjusted response rate of 30.9%. As GPs have different provider numbers for each practice, the number of GPs offering cervical screening services may have been overestimated. GP demographic details are summarised in *Table 1*. The majority (79.7%) of responding GPs reported being aware of the current National Health and Medical Research Council (NHMRC) guidelines and almost 60% (59.6%) reported that they always complied with the recommendations. Almost one-third (29.5%) of participating GPs reported that they 'always' received a clear follow-up plan from gynaecologists/colposcopists for patients following treatment of an HSIL. Overall, just over one-third (34.3%) of GPs were unable to identify all of the steps in the NHMRC's Test of Cure management pathway (*Table 2*).

There were identifiable factors associated with GPs' awareness of the Test of Cure management pathway (*Table 3*). Younger female GPs were more likely to be aware of the screening pathway when compared with male GPs aged over 55 years. Statistical differences in the awareness of the Test of Cure by the accessibility (metro, rural, remote) and socioeconomic status of the practice location were also analysed (*Table 3*).

Of the 34.3% of GPs who did not know the Test of Cure guidelines, the following comments were included with their surveys:

'I am unsure of HPV DNA testing'
'I know nothing about this test'
'I did not know this existed'
'I am not confident with this test or its follow-up at all'
'Unsure of guidelines on this; would this be offered by a specialist?'
'I don't offer it – I am uncertain where it fits in the management algorithm'.

Discussion

Our study specifically investigated the management of patients after treatment for CIN 2 and/or CIN 3, and identified that the majority of GPs did not 'always' receive a clear follow-up plan from the specialist ob/gyn to whom the patient had been referred. A proportion of GPs were unaware of these post-treatment best practice guidelines, which is inefficient. The use of co-testing (HPV DNA testing and cervical cytology) in general practice is a useful tool to identify patients with a history of HSIL, who are at the greatest risk of disease persistence/recurrence.[12,16]

The major knowledge gaps identified in this study include knowing when it was appropriate to perform HPV DNA tests and how to manage patients if they had two consecutive annual negative test results (2 x Pap smears and 2 x HPV DNA tests). We found that female GPs were more likely to be aware of the Test of Cure management pathway than male GPs. This difference may be a reflection of women's preference to see a female healthcare provider to discuss sensitive topics, and the GP's personal motivation to know the Test of Cure management pathway.

Our study's results and qualitative feedback suggest that there is a clear need for further education and promotion of using high-risk HPV DNA tests as a management pathway for GPs. The GP's armamentarium should include knowledge of how and when HPV DNA testing should be performed. GPs should have confidence in the use of this testing modality because, even if a cervical cytology test result is normal, the increased sensitivity of the HPV DNA test will detect high-risk HPV DNA types, indicating the presence of persistent cervical disease. Patients who successfully complete the Test of Cure should then be encouraged to return to routine cervical screening with a high degree of confidence.[5,10,12,16,17]

Table 2. Percentage of participants who answered selected items correctly	
Question	**Percentage correct (%)**
Q1 Factors considered most important when offering an HPV DNA test:	
• If the patient has received treatment for an HSIL	85.3
• The patient enquires about the test	40.5
• Test of Cure management pathway	44.1
Q2 Immediate guideline recommendation for patients who have received treatment for a HSIL? (colposcopy and Pap smear at 4–6 months post-treatment)	64.2
Q3 If the colposcopy and first Pap smear are both negative what is the next step for your patients? (Pap smear and HPV DNA test at 12 months post-treatment)	73.9
Q4 Once patients have had two consecutive annual tests (2 x Pap smears and 2 x HPV DNA tests) that are negative, what would be your recommendation for a patient? (return to routine (2-yearly) screening)	69.3
Correct answers are in parentheses where applicable	

This is beneficial, as the patient will not be required to return for annual screening.[15] Improved communication between the specialist ob/gyn and GP, through provision of clear follow-up instructions, will ensure GPs are equipped to provide patients with care that is effective and delivers a high level of surveillance.[15]

One of the limitations of this study was the low GP response rate (30.9%). However, it is well recognised that collecting information via surveys is difficult, specifically from physicians in the primary healthcare setting, and is challenging as time commitments may preclude GPs' participation in survey initiatives.[18–20] Nonetheless, the number of GP responses in our study has assisted in the

provision of the first preliminary insight into GPs' receipt of patient follow-up plans and their awareness of utilising co-testing (HPV DNA testing and cervical cytology) for patients who have been treated for an HSIL.

Given the benefits and importance of the Test of Cure management pathway, there is a role for professional development activities, such as workshops, conferences and online educational models, to provide GPs with contemporary knowledge of clinical practices in the area of cervical cancer prevention. Further efforts should be aimed at specifically enhancing GPs' skills in managing patients with cervical abnormalities detected through screening, and providing

information about high-risk HPV DNA testing. This information could assist GPs in transitioning these high-risk patients back to the recommended screening interval. There is also an opportunity for specialist obs/gyns who perform colposcopy and surgical procedures to assist GPs in the management of these patients by providing a clear follow-up plan for patients who have undergone treatment for an HSIL when they are discharged from specialist care.

Finally, future research investigating longitudinal health outcomes associated with women who have undergone and completed the Test of Cure is required. Studies performing economic modelling to determine potential cost savings by the reduction in annual cytology tests and colposcopic examinations are required. Australia was the first country to introduce the Test of Cure pathway in 2006 and is well placed to provide such evidence.[15]

Implications for general practice:

- GPs should have confidence in HPV testing, as it is a sensitive test that can detect the presence of high-risk HPV oncogenic types.
- When HPV testing is utilised in the management of patients post HSIL treatment it is eligible for a Medicare rebate.
- Co-testing can assist GPs in transitioning high-risk patients back to the recommended screening interval with a high degree of confidence.

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Table 3. Factors associated with GPs' awareness of the Test of Cure screening pathway

	Rate ratio	95% CI	P-value
Gender			
Female	2.3	1.6–3.2	0.000
Male (reference group)	1.0	–	–
Age (years)			
<35	1.4	0.7–2.5	0.315
35–44 (reference group)	–	–	–
45–54	0.8	0.5–1.2	0.327
≥55	0.5	0.3–0.8	0.002
Aware of NHMRC guidelines (Test of Cure)			
Yes (reference group)	–	–	–
No	0.5	0.3–0.8	0.003
Index of relative social disadvantage			
Most disadvantaged	0.6	0.2–1.4	0.215
More disadvantaged	1.2	0.6–2.2	0.644
Middle	1.9	1.2–3.2	0.012
Less disadvantaged	0.9	0.5–1.4	0.520
Least disadvantaged (reference group)	–	–	–
Accessibility/Remoteness Index of Australia			
Major city (reference group)	–	–	–
Inner regional	1.2	0.7–1.5	0.491
Outer regional	0.7	0.3–1.4	0.291
Remote/Very remote	0.9	0.4–2.0	0.838

Logistic regression was performed, estimating the odds of GPS being aware of the Test of Cure screening pathway.
CI, confidence interval

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Munro A, Codde J, Semmens J, Leung Y, Spilsbury K, Williams V, Steel N, Cohen P, Pavicic H, Westoby V, O'Leary P. **The Human Papillomavirus Test of Cure: A lesson on compliance with the NHMRC Guidelines on Screening to Prevent Cervical Cancer.** *A N Z J Obstet Gyn* 2015; 55(2): 185-190*.*

Original Article

The human papillomavirus Test of Cure: A lesson on compliance with the NHMRC guidelines on screening to prevent cervical cancer

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Background: In Australia, high-risk human papillomavirus (HR HPV) testing is recommended for follow-up of women treated for a high-grade squamous intra-epithelial lesion (HSIL). The sensitivity of HR HPV testing is critical to identify women at risk of further high-grade cervical disease. In Australia, this management protocol is known as the 'Test of Cure' (ToC).

Aim: To conduct a population-based study investigating practitioners' compliance with ToC.

Materials and Methods: Women treated for an HSIL between the five-year period 01 Jan 2006 to 31 Dec 2010 were identified and followed up for at least a 27-month period. Proportions and relative odds were determined for women entering and completing the ToC management pathway within recommended time frames.

Results: There were 5,194 women identified as 'eligible' to enter the ToC management pathway. Of these, 1,916 (37%) were managed with annual Pap smears and never had a HR HPV test performed. There were 1,296 (25%) women who entered the ToC management pathway within recommended time frames, and a further 1,978 (38%) women entered outside of the recommended time frames. Overall, 961 women completed the ToC and were classified as 'cured' and were eligible to return to two-yearly Pap smears. Women's demographic information was significantly associated with ToC commencement, specifically, age and year of treatment, and Index of Relative Socioeconomic Disadvantage.

Conclusion: Overall, a significant number of Australian women did not *enter* (~37%) and *complete* (~50%) the ToC management pathway. The challenge remains to advocate its use to practitioners to ensure women are returned to the population screening interval in a timely manner.

Key words: cervical, high-grade squamous intra-epithelial lesion, management.

Introduction

Women treated for a high-grade squamous intra-epithelial lesion (HSIL) remain at an increased risk of developing further cervical dysplasia and/or cervical cancer, and consequently, intensive follow-up protocols have been required.[1–4] Prior to 2005, the Australian management guidelines for post-treatment cytological surveillance for HSIL recommended annual cytological testing for life. In 2005, the National Health and Medical Research Council (NHMRC) introduced revised management guidelines recommending an alternative management pathway (Table 1) using high-risk human papillomavirus testing (HR HPV) in conjunction with cervical cytology as a 'Test of Cure' (ToC).[1] This management pathway returns eligible women back to routine screening (two yearly) and reduces previously required post-treatment surveillance frequency.[1] Multiple follow-up studies have shown HR HPV testing to be efficacious for detecting residual or recurrent disease inpatients treated for HSIL.[5–11]

A ToC involves cervical cytology and HR HPV testing at 12 and 24 months post-treatment. If both sets of the cervical cytology and HR HPV tests are negative, then a woman is considered to have completed her ToC, and advised to return to the routine cervical screening interval.[1] However, should any of the cytology or HR HPV tests remain abnormal during post-treatment surveillance, the woman is encouraged to continue with cotesting every 12 months until two consecutive negative cytology and HR HPV tests 12 months apart occur[1] (Table 2).

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Table 1 Australian Test of Cure management pathway for women treated for an high-grade squamous intraepithelial abnormality (HSIL)

Post-HSIL treatment	Pap smear	Colposcopy	HPV testing
4–6 months	√	√	
1st set of tests at 12 months	√	–	√
2nd set of tests at 24 months	√	–	√

Continue cervical cytology and HPV testing every 12 months until these tests are both negative on two consecutive occasions.

Table 2 Test of Cure potential annual cotesting (cytology and HR HPV) outcomes

12 months	24 months	36 months	Test of Cure outcome
C0 H0			Incomplete
C0 H0	C0 H1	C0 H0	Incomplete
C1 H0	C0 H0	C0 H0	Complete
C0 H0	C0 H0		Complete
C0 H0	C1 H1	C0 H0	Incomplete

C0 = normal cytology, C1 = abnormal cytology, H0 = HR HPV negative, H1 = HR HPV positive.

The primary objective of this study was to confirm whether women treated for an HSIL are entering the ToC within the recommended time frames, the number of women who have the second set of cotests performed and the number of women who successfully completed the ToC. The secondary objective was to explore patient-related factors that influenced participation in the ToC management pathway.

Materials and Methods

This was a retrospective cohort study that followed up women from time of HSIL treatment (ie excision or ablative therapies) until their last cervical test result, hysterectomy or death record. The Cervical Screening Register (CSR) of Western Australia (WA) was used to identify the study cohort. The CSR is legislated to compile all cervical test results (HPV, cervical cytology and histology) for women who reside in WA. Cervical test results were classified according to the Australian Modified Bethesda System 2004.[1]

A deidentified extraction of Hospital Morbidity Data System (HMDS) records and death registry records for these women was obtained from the Western Australian Data Linkage System for 01 Jan 2006 to 31 Dec 2010. The HMDS records all discharge summaries from all Western Australian acute hospitals (private and public) and day surgery clinics. In the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification (ICD-10-AM), codes were used to identify cervical dysplasia and relevant procedural codes (ie hysterectomy).

Table 3 Women's demographic information

	Number of women (*n* = 5,194)	Percentage (%)
Age (years)		
≤24	1,385	26.7
25–34	2,396	46.1
>35	1,413	27.2
Treated lesion grade		
CIN2	2,161	41.6
CIN3	3,033	58.4
Referral Pap smear† (screened within two years prior to treatment)		
Unsatisfactory	22	0.4
Normal	135	2.6
Possible LGEA/LGEA	777	15.0
Possible HGEA	1,105	21.3
HGEA/Invasive	3,107	59.8
No referral Pap smear result‡	48	0.9
Treatment performed		
Excisional treatment		
Cone biopsy or LOOP/LLETZ	4,995	96.2
Ablative treatment		
Radical diathermy/laser destruction/other destruction of the cervix	199	3.8
Pap smear result post treatment (within 3–7 months of treatment performed)		
Unsatisfactory	42	0.8
Normal	2,579	49.7
Possible LGEA/LGEA	356	6.9
Possible HGEA	33	0.6
HGEA	72	1.4
Pap smear occurred outside 3–7 months	2,073	39.9
No post treatment Pap smear result†	39	0.7

†Most severe Pap smear test result was reported for the defined period. ‡Although women may have been identified as not having a Pap smear result post treatment within 3–7 months, they may have been followed up earlier or post seven months.
LGEA = low-grade epithelial abnormalities; HGEA = high-grade epithelial abnormalities; LLETZ = large loop excision of transformation zone; CIN = cervical intraepithelial neoplasia.

Ethical approval was granted from the Human Research Ethics Committees of the Western Australian Department of Health (ethics research project number: 2012/49) and Curtin University (ethics research project number: HR 86/2012).

The CSR was used to identify women aged 18 years or more with histological confirmation of an HSIL for the period 01 Jan 2006 to 31 Dec 2010. The woman's full screening history was reviewed to confirm incident cases of HSIL. All women were followed up until (May 2013)

Table 4 Logistic regression results investigating women's relative odds entering the Test of Cure management pathway within recommended intervals

	Odds ratio	95% confidence interval	P-value
Age (years)			
≤24 (base)			
25–34	1.1	0.9–1.3	0.601
>35	1.3	1.1–1.6	0.011
Year of treatment			
2006 (base)			
2007	0.8	0.6–1.1	0.109
2008	1.1	0.9–1.4	0.382
2009	1.4	1.1–1.7	0.007
2010	1.6	1.36–2.0	0.000
IRSD†			
Most disadvantaged	0.7	0.5–0.9	0.017
More disadvantaged	0.9	0.7–1.1	0.298
Middle	0.9	0.7–1.1	0.305
More advantaged	0.9	0.8–1.1	0.423
Most advantaged (base)			

†Index of relative socioeconomic disadvantage.

to allow a post-treatment follow-up time of at least 27 months. All diagnoses of HSIL in this study refer to pathologists' histopathologic interpretations of surgical pathology specimens, including cervical biopsies endocervical curettage specimens, and/or therapeutic excisional procedures.

Women were excluded if a hysterectomy was performed as their initial treatment or if they had histological confirmation of an adenocarcinoma in situ (AIS), or cervical cancer.

Demographic information and previous cervical screening history were obtained for all women. Age at treatment was categorised into 10-year age groups. Postcode of residence at time of treatment was used to assign a socioeconomic level using Australian Bureau of Statistics 2006 Indices of Education and Occupation (IEO), Relative Socioeconomic Disadvantage (IRSD) and Economic Resources (IER).[12] Postcodes were also used to allocate a 2006 Accessibility/Remoteness Index of Australia (ARIA+) category.[13]

In the majority of cases, the HR HPV test and cervical cytology occurred at the same time; however, in some instances (eg the woman had an unsatisfactory Pap smear or HR HPV test), they may not have occurred on the same date. Therefore, cotests were identified if either of the tests occurred within 60 days of each other.

The HR HPV result was recorded as either HR HPV detected, not detected or unsatisfactory sample. Specific HR HPV subtypes were not recorded in this study. A concurrent positive cytology result was defined as a low-grade squamous intra-epithelial lesion (LSIL) or higher severity.

Adherence to Test of Cure guidelines

To investigate women's compliance with ToC guidelines, they were classified as (i) ToC nonstarters (never had a HR HPV test performed); (ii) commenced ToC within recommended guidelines; or (iii) commenced ToC outside recommended guidelines. These categories were developed to support the NHMRC's *Guidelines for the Management of Asymptomatic Women with Screen Detected Abnormalities*. These Guidelines advise that women treated for an HSIL require colposcopy and Pap smear at 4–6 months following treatment. Cotesting (cervical cytology and HR HPV) should then be performed at 12 months post-treatment and annually thereafter until both tests are negative on two executive occasions. For this analysis, follow-up time frames were defined as 12 and 24 month periods. A time extension of three months on either side of the 12- and 24-month period was incorporated to allow women adequate time to return for their screening tests. This time extension also took into consideration laboratory and cervical screening register processing and reporting times.

A woman was determined to have completed the ToC if she tested negative on her Pap smear and negative for HR HPV on two consecutive occasions (Table 1). If a woman had a cervical abnormality or tested positive for HR HPV, the ToC time frame was reset to start from the next first set of negative cotests (Table 2). Women were classified as having undergone ToC cotests within the recommended time frames or outside the time frames. Women who did not undergo any ToC cotesting were considered ToC nonstarters, while women who did not return for the second or subsequent cotests within the time frame were considered to be ToC non-completers.

Post-ToC disease persistence and/or progression was investigated and defined as a high-grade histology result such as an HSIL (cervical intra-epithelial neoplasia grade 2 or 3) or AIS. Disease progression was classified as cervical cancer. Histology results were classified to the most severe histological abnormality found.

Logistic regression models were constructed to investigate whether women's social, demographic and health-related factors were associated with starting the ToC pathway within the recommended time frames. A binary variable was created that divided women into those who commenced ToC within recommended time frames and those who did not. Women who did not start the ToC process were not included. Variables included in the modelling process were age and year of treatment, accessibility index and socioeconomic status. Statistical significance was determined as a *P*-value <0.05, and the 95% confidence intervals (CI) for odds rate ratios were calculated. Plausible interaction terms were tested using likelihood ratio tests. Goodness-of-fit tests were used to assess model suitability. STATA/IC 13.0 (STATA Corporation, College Station, TX, USA) was used for data manipulation and statistical analysis.

Results

For the study period, 5,453 women were confirmed to have received treatment for HSIL; however, 259 women did not have a record of any further follow-up data post-treatment and were considered 'lost to follow-up'. The remaining 5,194 women were identified as 'eligible' to undergo the ToC management pathway, and their first two post-treatment screening histories were investigated (Fig. 1). Of these, 61 women were confirmed to have had a hysterectomy, and a further eight women had died during follow-up period. The mean age at time of HSIL treatment was 30.9 years (range 18–87 years). Most women (96%) were treated with excisional procedures, and the remainder (4%) were treated with ablative procedures (Table 3).

Of the 5,194 women who were eligible to undergo the ToC, 1,916 (37%) only had subsequent Pap smears and no record of HR HPV tests performed post-treatment. These women were considered ToC nonstarters. Of the ToC nonstarters, 1,460 (76%) had normal cervical cytology results post-HSIL treatment and continue to have annual Pap smears. All women who were treated for an HSIL remain eligible to enter the ToC management pathway to support their return to the routine (two yearly) population-based screening interval.

There were 1,296 (25%) women who had their first pair of cotests performed between 9 and 15 months post-HSIL treatment. At first annual follow-up, 336 women tested positive for HR HPV and/or cervical abnormality and had to restart the ToC process.

A further, 960 (74%) tested negative for both the cervical cytology and HR HPV. Of the 960 women who tested negative for their first set of cotests, there were 449 women who returned for cervical cytology but no second HR HPV test was performed. There were 286 women who returned for their second set of cotests within the recommended time frames with 281 (22%) completing ToC following a second set of negative results.

Although outside the recommended time frames, a further 225 women returned for their second set of cotests. Of the 1,296 women, there was no further follow-up data available for 39 women post the first set of cotests.

Of those eligible, 1,978 (38%) women commenced ToC outside the recommended interval (eg >15 months post-treatment). Of these, 1,415 women tested negative for a cervical abnormality and/or HR HPV and 563 (28.5%) tested positive for their initial cotest. However, there were 861 women who returned for cervical cytology HR HPV test. Overall 98 (<10%) women had no further follow-up data available post the first set of cotests.
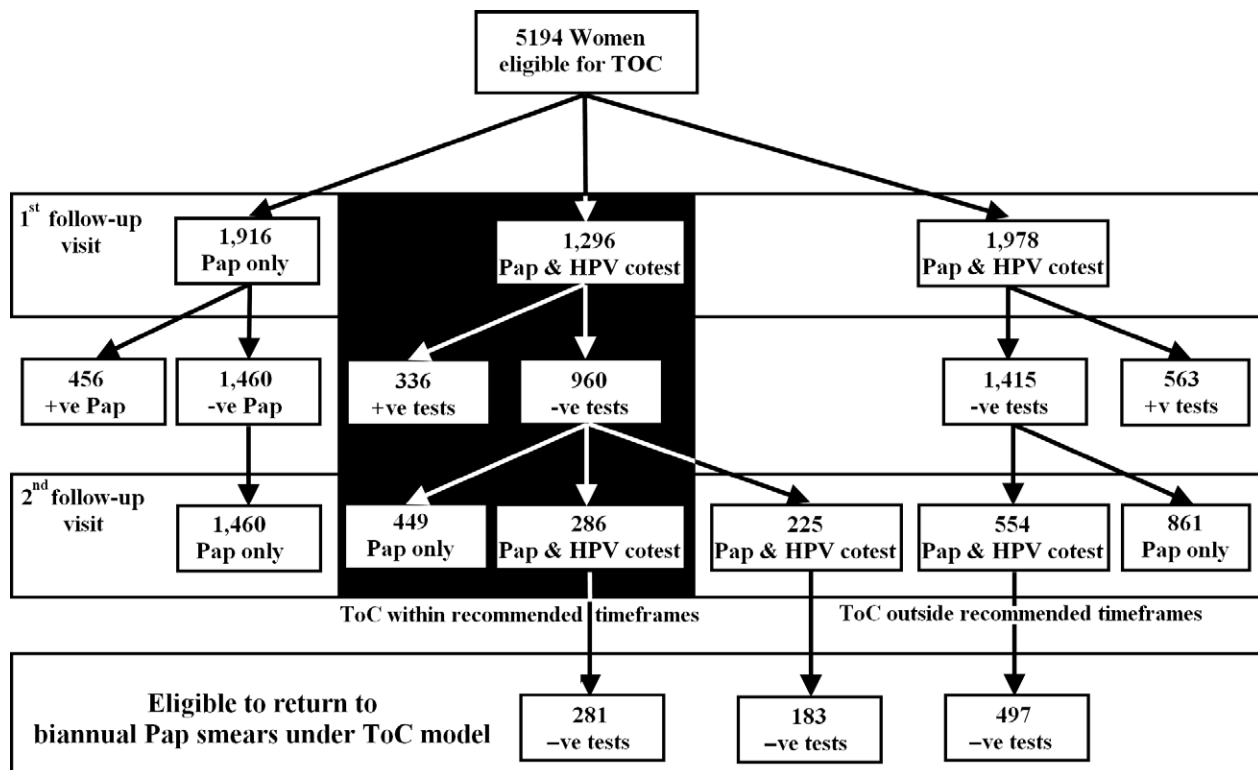

Figure 1 This flow diagram indicates the number of women who tested negative for both sets of cotests and was eligible to return to biannual cervical screening. The follow-up of women who tested positive is not shown.

Of the 3,274 women who commenced the ToC management pathway, 961 (29%) women successfully completed the ToC and all were identified as 'cured'. There were a further 441 (13.5%) women who commenced the ToC; however, they tested positive (on either their initial or second set of cotests) and are yet to test negative on two sets of consecutive tests (cervical cytology and HR HPV). There were no subsequent disease persistence or progression histology test results recorded for the ToC completers in the remaining follow-up time (the median follow-up time was 2.3 years, range <1 year to 5 years) although longer follow-up is required.

Logistic regression models were constructed to identify factors associated with whether a woman ($n = 3,274$) entered the ToC pathway within recommended time frames or not, regardless of their ToC test finding (Table 4). Women aged >35 years were found to be more likely to enter the ToC management pathway compared to women aged <25 years (OR 1.3, 95% CI 1.1–1.6). Year of treatment was also identified as a significant factor with a positive trend indicating increased compliance. Women treated in 2010 were 1.6 times more likely (95% CI 1.3–2.0) to enter the ToC at the recommended time frame compared to women treated in 2006. Socioeconomic status was also a significant factor with women classified as 'most disadvantaged' 30% less likely to enter ToC at the recommended interval compared to women classified as 'least disadvantaged' (OR 0.7, 95% CI 0.5–0.9). Accessibility and whether the original HSIL lesion was classified as CIN2 or CIN3 were not associated with commencing ToC within the recommended time frames.

Discussion

This is the first population-based Australian study to investigate the utilisation of HR HPV as a cotest for women post-treatment for HSIL through linked person administrative data sets. The study found that over 50% of women who commenced the ToC management pathway did not have the second HR HPV test performed and consequently did not achieve a 'cured' status. These women continued to have annual Pap smears and potentially unnecessary biopsy and/or colposcopy investigations. The study also revealed that a large proportion of women (~37%) did not have a HR HPV tests performed post-treatment despite the NHMRCs Guidelines introducing HR HPV testing as a cotest with conventional cytology in 2006. This is a particularly important finding for Australian policy makers, given Australia is going to be implementing significant policy changes to the current screening pathway.

The number of women entering the ToC management pathway continues to increase yearly, and healthcare providers should be commended and encouraged to manage women in accordance with these best practise guidelines. Practitioners may be unaware that HR HPV testing is performed in a similar way to performing a Pap smear, using a swab or bush which collects cells from the cervix. Rather than smearing the sample collected onto a microscope slide (conventional Pap smear), the head of the spatula is broken off and placed into a small glass vial containing preservative fluid, or rinsed directly into a preservative fluid. The vial is then transported to the laboratory for processing.

Consequently, it is possible the slow uptake of the ToC management pathway amongst practitioners highlights the importance of early community engagement and planned educational programmes when changes to guidelines are introduced.

Our study also confirmed that there were more women completing the ToC outside the NHMRC recommended time frames. Given the overall treatment success within this cohort, Australian healthcare providers involved in the follow-up care of women need to be aware of and adhere to the ToC management pathway. This will ensure women's timely and safe return to routine screening (currently two yearly).

The results here indicate that an overall low ToC completion rate is similar to findings recently reported in a New South Wales retrospective study.[9] As reported by Morrell and Qian, it is possible that general practitioners and other women's health clinicians believe that a single HR HPV-negative test result, along with successive negative cytology, is sufficient to indicate successful treatment. However, Munro *et al.* surveyed general practitioners found 30% of responding GPs had no or limited knowledge of ToC. A clear need exists for gynaecologist/colposcopists to provide referring GPs (and their patients) with a clear discharge summary that outline required time intervals for follow-up screening and the rationale that supports this.[14]

This study has confirmed the importance of women's demographic information that supports a timely ToC commencement. A rural address was not found to be a barrier to compliance in a ToC management plan. However, younger women (aged <35 years) and women living in areas of lower socioeconomic status were found to be at risk for not entering the ToC management pathway. Healthcare providers who are involved in the management of these women play a critical role in explaining the importance of having two consecutive cotests and the role of HR HPV testing. By explaining the benefits of ToC, including confirmation of oncogenic HPV clearance, decreased unnecessary referrals to colposcopists/gynaecologists (less unnecessary psychological stress and lower financial costs) may further encourage follow-up attendance. Additionally, if the practitioner is uncertain of a patient's medical history, Australian State and Territory cervical screening registries can usually provide comprehensive cervical screening histories for patient's to guide subsequent testing.

This study has important strengths. Firstly, it used a state-wide population cervical screening register with virtually complete coverage since late 1994 and we have increased confidence that all women with histological confirmation of an HSIL were identified. Additionally,

through linked hospital morbidity, cancer and death records, women who were no longer eligible to complete the ToC (eg women who had a hysterectomy or were deceased) could be excluded. Limitations of the study included those women who were lost to follow-up were nonassessable, and we were unable to investigate whether the impact of the woman's socioeconomic status was confounded by patient care being delivered by a specialist verse GP after their original surgery. A further limitation of this study is the well-acknowledged inherent error that exists in all databases, which can never entirely be eliminated. However, the CSR of WA routinely carries out quality assurance (QA) processes to ensure high-quality data capture and completeness is obtained. The QA processes employed ensure the level of error within the CSR of WA is acceptable.

In this study, we confirmed a high rate of treatment success and that no disease persistence or cervical cancer incidence occurred for any woman who completed the ToC within the limited follow-up time. To strengthen these findings, several more years of follow-up data are required. Nonetheless, the absence of cervical disease persistence and cervical cancer after completing ToC is a positive and reassuring finding to healthcare providers involved in the post-treatment management of these women.

Acknowledgements

Disclosure of Interests

Two authors (A Munro and N Steel) are employed at the WA Cervical Cancer Prevention Program that is responsible for maintaining and operating the Cervical Screening Register of WA.

Details of Ethics Approval

Study data were obtained in June 2013 following approval from the Curtin University Human Research Ethics Committee (ethics research project number: HR 86/2012) and the Human Research Ethics Committees of the Western Australian Department of Health (ethics research project number: 2012/49).

Funding

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Chapter 6:

Discussion

Since the release of the NHMRC Guidelines in 2005, several studies have provided new and updated findings regarding the awareness and management of women with abnormal cervical cell histology. As a consequence it is timely for these guidelines to undergo a review[3, 97, 98].

This thesis and its publications aimed to provide up-to-date data that can support the revision of the NHMRC Guidelines and further contribute to sound clinical evidence. The updated NHMRC Guidelines will assist clinicians in providing education to their patients regarding age-related management strategies (i.e. surveillance versus immediate treatment) and importance of co-testing (HPV and cervical cytology) after treatment of high-grade cervical lesions, in turn reducing the number of follow-up visits, alleviating potential patient fears, and reducing unnecessary anxiety.

As GPs are at the cold face in delivering cervical screening services to and following-up women with cervical abnormalities, two publications were developed to provide clinically relevant and evidence-based information to GPs. These articles were purposely submitted and subsequently published by the *Australian Family Physician* to further assist GPs in their delivery of the highest quality patient care based on best practice. Clinician adherence to revised Australian management and follow-up guideline recommendations, delivery of patient education, and appropriate referrals will be essential in the initial detection and successful treatment of early cervical changes.

6.1 Strengths and limitations

The strengths and limitations specific to the individual studies are discussed in detail in the discussion section of each publication, this section provides a more holistic overview.

A major strength of this work was it was based on large administrative databases from a stable and isolated WA population[73]. This results in almost complete case ascertainment with minimal loss to follow-up over the study period and study findings are externally valid to the wider Australian context. This is of critical importance when investigating rare cervical pathologies (i.e. AEC and ACIS (Publication 1 and 2) and when women's longitudinal health outcomes are investigated (Publication 1, 2, and 3). The large sample sizes also allowed investigation into multivariate models controlled for multiple risk factors and potential confounders simultaneously.

As this research was able to use population-based administrative datasets (Publications 1, 2, 3, 4), the limitations of this thesis are related to its retrospective observational design. These issues were discussed in further detail in Chapter One. As with all retrospective studies, the work reported in this thesis that utilised administrative data also has a number of constraints. Examples include the quality of the data (e.g. data reliability/completeness) and potential confounding variables not present in the datasets (e.g. women may have been symptomatic, on medication, e.g. contraception; lifestyle factors, e.g. multiple sexual partners, high parity etc.) and lack of other relevant clinical details. Attempts were made to address some of these potential short comings, for example within the ACIS Publication, a manual review of all women's histopathology variables was conducted to collect critical treatment information (i.e. specimen depth, margin clearance (yes, no, or undetermined), specific margin involvement (i.e. endocervical, ectocervical, or both) in the lesion, and the presence of another lesion type present (i.e. CIN and ACIS) etc.).

Similarly while the administrative data provided readily accessible information about GP compliance rates with the ToC, it could not provide details on GP knowledge and awareness of this management pathway. This data needed to be acquired through dissemination of a survey (Publication 4). The major limitation of the survey was selection and response bias, as the GPs may or may not have reported positive compliance rather than reporting non-compliance with the Guidelines. Additionally the response ratio also needs to be considered when interpreting the survey data. Although the survey response rate was 30% of all GPs in WA (including the rural and metropolitan areas), the survey results further supported the quantitative population-based findings and further reinforced the importance of GPs being provided with educational tools and promotion of the ToC management pathway (Publication 5).

6.2 Key findings and their clinical significance

The major topics presented in this thesis encompass three broad themes: the clinical significance of low-grade glandular lesions (Objective I), management of women with glandular lesions (Objective II) and treatment of young women with CIN2 (Objective III) and practitioner's awareness/knowledge, and compliance with recommendations for the follow-up of women treated for CIN2/3 (Objective IV). The major findings from each research objective are discussed below.

6.2.1 Clinical significance of AEC

The clinical importance of the test for AEC (Objective I) and revealed its implications for women (i.e. presence of a high-grade cervical abnormality or gynaecological malignancy) were investigated in Chapter 3. This was a novel study both nationally and internationally, so the results are unique when compared to those of previously published studies.

Importantly, the study confirmed that a positive test result for AEC definitively warrants further investigation for both cervical and endometrial abnormalities. This is especially important for younger patients with a) no cervical screening history or b) low-grade cervical disease and for older women (40 years) to exclude endometrial pathology. In future, the Federal Health Department of Australia is expected to mandate five-yearly cervical screening using the HPV test as the primary cervical screening test; however, reflex liquid-based cytology testing will be performed for women with a positive result for the HR HPV test. Consequently, reflex cytology tests may still report the presence of AEC and thus the findings from this study are still highly applicable in the Australian setting.

6.2.2 Effectiveness of conservative treatment for women histologically confirmed with ACIS

Conservative treatment of ACIS remains controversial both within Australia and overseas[3, 32, 33, 40, 41, 79 81-87]. For women who have completed their childbearing, total hysterectomy remains the treatment of choice for the following reasons:

- Extension into the endocervical canal is frequent and determination of the desired depth of excision can be difficult.
- ACIS can be multifocal and discontinuous in nature, so negative margins on an excision specimen do not provide 100% assurance that the lesion has been completely excised.
- Invasive cervical cancer cannot be confirmed unless a diagnostic excisional procedure is performed.

For younger women, especially as the incidence of ACIS in this age group continues to increase[2], investigation into conservative treatment options and their associated health outcomes is necessary. As such, this thesis used linked health administrative data coupled with a comprehensive histopathology review of all women with biopsy-confirmed ACIS (Objective II) within WA to report their health

outcomes after conservative treatment. Positively, the study did not find a significant difference in health outcomes for women that were treated by LEEP and those treated with CKC biopsy. Therefore, this thesis is in agreement and supports the *2012 ASCCP Guidelines* and recommends that the NHMRC Guidelines be amended to include the following: *In cases of women with biopsy-confirmed ACIS that desire future fertility, conservative treatment with LOOP/LLETZ is an acceptable treatment modality for carefully selected patients (i.e. patients that can comply with follow-up instructions).* Additionally, follow-up recommendations for these patients should include the following:

- Re-excision of the lesion is recommended if the margins of the specimen are positive (i.e. CIN and/or ACIS is involved)
- Counselling of patients treated conservatively is imperative to ensure they attend long-term follow-up investigations.
- Patients should be followed-up at six months and undergo co-testing (HPV and cervical cytology, specifically endocervical sampling) in conjunction with colposcopy.

Updating the NHRMC Guidelines to include a specific management protocol will greatly assist clinicians in managing women with biopsy-confirmed ACIS that wish to preserve fertility and are able to adhere to rigorous follow-up throughout this time period.

6.2.3   Importance of spontaneous regression of CIN2 for young women

Clinicians were provided with further evidence in Chapter 4 (Objective III) to support the adoption of a conservative approach (i.e. surveillance) for young women with histologically confirmed CIN2 (approximately, 60% show spontaneous regression). To date, this is the largest population-based cohort of young women (n = 924) that analysed follow-up data for two years. Clinicians can be confident that those women who undergo comprehensive counselling and agree to adhere to follow-up protocols can be managed conservatively without risk of progression in a two-year period (i.e. CIN2 in young women behaves as a low-grade lesion).

Importantly, the study's findings and conclusions were consistent with current guidelines of the *2012 American Society for Colposcopy and Cervical Pathology (ASCCP)*, which support conservative management of young women. However, a larger study (cohort and prospective design) is still needed to validate this

approach. It is hoped that these study findings will support the revision of the NHMRC Guidelines to ensure all Australian clinicians involved in the management of young women with CIN2 are aware of the benefits/risks of treating versus surveillance management approaches.

6.2.4 Practitioner's awareness/knowledge of and compliance to ToC

Women with CIN2/3 are treated by local excision or ablation to prevent progression to cervical cancer. Although conisation is proven to be an effective treatment for removing CIN, it does not necessarily lead to elimination of the HPV virus. Clinician's awareness of HR HPV testing as outlined by the NHMRC Guidelines is a key step in ensuring the best patient outcomes but this relies on practitioner compliance to the recommendations. GPs' awareness/knowledge and subsequent compliance (Objective IV) in managing women in accordance with the ToC management pathway was found to be very low in Chapter 5. This finding confirmed a similar observation in a recent study performed in New South Wales[52].

Clearly there is a need to provide GPs with ongoing education in the delivery of these (and future revised guidelines). To this end, the findings from the survey and population-based analysis were shared with the NCSP Program managers' who will look for opportunities to further promote this pathway among health care providers involved in the management of women. Since these findings were obtained, ToC has been promoted at a Western Australian Pap Smear Provider Professional Development day (for metropolitan and rural health care providers), promoted in the *Medical Forum and Medical Observer.* It is hoped that further education sessions will be delivered to GPs in future.

6.3 Implication of research findings

The research findings obtained in this thesis have been presented at local, national, and international meetings. At a local level, the findings have been shared with the WA Cervical Cancer Prevention Program (WACCPP) as well as at the professional development sessions that the WACCPP provides to health care providers that provide cervical screening services. Additionally, this research has been utilised to further enhance (provision of clinically up-to-date information of i.e. pathogenesis of cervical cancer and its precursors, classification of cervical abnormalities etc.) the WACCPP's website content (Additional material 1) which is accessible by health care providers and consumers.

At the national level, research findings have been shared with the National Cervical Screening Program managers' ensuring dissemination to other states and territories. This has facilitated effective completion of the research feedback loop (i.e. other States and Territories will work towards developing new research initiatives that builds on our existing evidence).

Three studies (Publication I, IV and V) were published in Australian medical and obstetric/gynaecology journals to further support Australian practitioners in the management of women with cervical abnormalities. These were critical forums and will inform the revision of the 2005 NHMRC Guidelines (to be completed by 2017) in support of the implementation of a revised cervical screening pathway.

Internationally, some of these findings were presented at the *International Gynecological Cancer Society Meeting* and the *2014 World Cancer Congress* as well as published in a high-ranking international gynaecology journal (Publication II).

6.4 Future avenues for research

In the Australian landscape, the value and importance of "big data" has long been acknowledged and there is a clear necessity to develop and capitalise on the availability of these data through innovative linkage/integration processes. The work in this thesis has started to explore some of the large body of linked population-level data that can support the Australian National Cervical Screening Program as it enters an era of great change. The Australian Government is working collaboratively with the states and territories to develop a National Cancer Screening Register that will support the delivery of the national cervical and bowel screening programs to be effective 1 May 2017. Establishment of this national register would enhance data integration/sharing (e.g. collection of cervical screening test results, HPV vaccination status, collection of colposcopy outcomes etc.) and has the potential to:

- Provide "one woman, one record" – allowing health care providers to access a women's complete screening history in one central system
  - o Provide predictive analytics to more effectively identify early treatments in a patient's history, to prevent future medical events and avoid future readmissions.
  - o Incorporate family history and current health conditions for increased effective pre-emptive care.

- o Decrease cross border issues e.g. assists in managing and following-up the eligible population more efficiently.
- Eliminate costs of maintaining and storing duplicate health records.
- Provide researchers with access to increased sample sizes (e.g. national population data) that could be used to investigate rare events (e.g. incidence and treatment of small cell carcinoma); including effectiveness of different treatment modalities, post surgical management strategies and longitudinal health outcomes associated with these diseases.

However, it is important to acknowledge the success of the current Australian CSRs and consider the potential pitfalls of attempting to implement a national system, such as:

- Loss of State specific initiatives (e.g. data cleansing for Aboriginal health services or provision of individualised data requests).
- Potential for failure of the national register and the subsequent implications that could occur for women.
- Loss of jurisdictional knowledge and expertise (e.g. manual data cleansing).
- Potential loss of jurisdictional quality assurance processes that ensure data completeness and validity (e.g. collaborative relationships with laboratories in the codification of cervical test results and timely transmission of data).

It is of critical importance to be aware that should a national cancer register be developed, it must possess increased functionality and capability (when compared to existing jurisdictional cervical screening registers) to store patient's demographic information and medical records, and would need to be prepared/developed systematically. This would ensure that data collected is of a high quality to support delivery of patient care (e.g. patient follow-up of abnormal test results) and possess the potential to translate into meaningful research initiatives (e.g. monitoring the safety of extended screening intervals). Future studies utilising 'big data' obtained from a national cancer-screening registry should focus on meaningful and objective criteria, such as clinical and social effectiveness, and interventions that can improve efficiency of service delivery.

Key areas of further work stemming from this thesis included investigation into the management of young women (aged < 25 years). Specifically, could patients

with CIN3 lesions be left untreated and remain under surveillance to allow spontaneous regression? Studies that report the safety of observation for young women with histologic CIN3 are needed, as long-term outcomes after apparent regression without treatment remain currently unknown.

Other studies that examine the long-term follow-up data to help inform post-treatment outcomes and optimal long-term follow-up intervals for women with treated for CIN2/3 are required. This work could detail when women could "safely" return to a routine screening interval and inform the future NHRMC Guidelines.

Finally, the effect of the HPV vaccination on large populations of women over long periods of follow-up is yet to be fully studied. Research is required to determine whether HPV vaccination alters the natural history and/or management of cytologic or histologic abnormalities?

6.5 Achievements against thesis objectives

The work of this thesis set out to investigate three broad areas of interest including diagnosis and clinical significance of low-grade glandular abnormalities, treatment and management of women with high-grade cervical abnormalities. The work was defined by 4 specific objectives:

Objective 1: Investigate the risk factors and incidence of atypical endocervical cells of undetermined significance for Western Australian women in Pap smear test results and the associated health outcomes.

Objective 2: Analyse linked population-based administrative data to evaluate women with histologically confirmed ACIS managed with conservative treatment in WA.

Objective 3: Utilise linked population-based administrative data to investigate the spontaneous clearance rate among young women (aged <25 years) with histologically confirmed CIN2.

Objective 4: Determine practitioners' knowledge, awareness, and compliance with the Test of Cure management pathway.

In addition, it was hoped this work would help inform the revision of the NHMRC Guidelines for the management of women with rare cervical pathologies and to identify areas requiring further improvement, which is due for release in 2017.

To this end, work that has underpinned each objective has resulted in at least one publication in a peer-reviewed journal, presentation at national and international conferences and further dissemination to appropriate state and national bodies. As such, it is believed that by these measures the outcomes of this thesis have been achieved.

6.6 Vision for future research initiatives

As this thesis draws towards completion, I look forward to starting a new chapter within my early research career. I believe that I was awarded a great privilege to have worked with experts in the field of clinical sciences, specialists that are interested and committed to improving women's health and those who have been involved in utilising "big data" for many years.

Through valuing these relationships and working collaboratively across multi-disciplines, we were able to investigate research questions that resulted in translational clinical findings for the Australian female population. As science is a dynamic field and continues to evolve at a significant pace, I am excited to further contribute to emerging knowledge that may improve women's health outcomes, specifically in the area of gynaecology oncology.

This thesis has only commenced exploration into a potentially very large body of population-based work that needs to be conducted in support of women with gynecological disease. Consequently, I have commenced discussions with the WACCPP and other research institutions (i.e. King Edward Memorial Hospital, Saint John of God Hospital) to further identify gynecological research priorities that are yet to be investigated. It is my hope that through utilising "big data" inconjunction with chart reviews, we will be able to positively contribute to an ever-growing evidence base that supports women with gynaecological conditions such as cervical, ovarian and/or endometrial cancer.

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Appendix 1: Statement of Contribution of Others
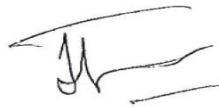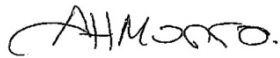
To Whom It May Concern

I, Aime Munro, contributed to concept development, data collation, analysis and manuscript preparation in the following publication:

Munro A, Williams V, Semmens J, Leung Y, Stewart CJR, Codde J, Spilsbury K, Steel N, Cohen P, O'Leary P. **Risk of high-grade cervical dysplasia and gynaecological malignancies following the cytologic diagnosis of atypical endocervical cells of undetermined significance: A retrospective study of a state-wide screening population in Western Australia.** *A N Z J Obstet Gyn* 2015; 55(3): 268-73.

I, as a Co-Author, endorse this level of contribution by the candidate indicated above is appropriate.

James Semmens

Jim Codde

Vincent Williams

Yee Leung

Peter O'Leary

Nerida Steel

Paul Cohen

Katrina Spilsbury

To Whom It May Concern

I, Aime Munro contributed to concept development, data collation, analysis, and manuscript preparation in the following publication:

Munro A, Leung Y, Spilsbury K, Semmens J, Codde J, O'Leary P, Williams V, Steel N, Cohen P. **Comparison of cold knife cone biopsy and loop electrosurgical excision procedure in the management of cervical adenocarcinoma in situ: What is the gold standard?** *Gynecol Oncol* 2015; 137(2): 258-63.

I as a Co-Author, endorse this level of contribution by the candidate indicated above is appropriate.

James Semmens

Peter O'Leary
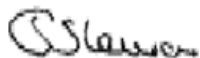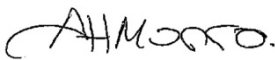
Jim Codde

N

Vincent Williams

Paul Cohen

Yee Leung

Katrina Spilsbury

Colin Stewart

To Whom It May Concern

I, Aime Munro contributed to concept development, data collation, analysis, and manuscript preparation in the following publication:

Munro A, Powell R, Cohen P, Bowen S, Spilsbury K, Codde J, Semmens J, O'Leary P, Williams V, Leung Y. **Evidence for spontaneous regression of cervical intraepithelial neoplasia-grade 2 in young Western Australian women: A review of 2,692 cases.** Accepted by Acta Obstetricia et Gynecologica Scandinavica (manuscript number: AOGS-15-0599.R1).

I as a Co-Author, endorse this level of contribution by the candidate indicated above is appropriate.

James Semmens

Peter O'Leary

Jim Codde

Nerida Steel

Vincent Williams

Paul Cohen

Yee Leung

Katrina Spilsbury

Rhys Powell

To Whom It May Concern

I, Aime Munro contributed to concept development, data collation, analysis and manuscript preparation in the following publication:

Munro A, Codde J, Semmens J, Spilsbury K, Williams V, Steel N, Cohen P, Pavicic H, Westoby V, O'Leary P. **Utilisation of co-testing (human papillomavirus DNA testing and cervical cytology) after treatment of CIN: A survey of GP's awareness and knowledge.** *AFP* 2015; 44(1): 64-8.

I as a Co-Author, endorse this level of contribution by the candidate indicated above is appropriate.

James Semmens

Peter O'Leary

Jim Codde

Nerida Steel

Vincent Williams

Paul Cohen

Yee Leung

Katrina Spilsbury

Heidi Pavicic

To Whom It May Concern

I, Aime Munro contributed to concept developemtn, data collation, analysis and manuscript preparation to the publication:

Munro A, Spilsbury K, Leung Y, O'Leary P, Williams V, Codde J, Steel N, Cohen P, Semmens J. **The Human Papillomavirus 'Test of Cure': A lesson on compliance with the NHMRC Guidelines on Screening to Prevent Cervical Cancer**. *A N Z J Obstet Gyn* 2015; 55(2): 185-90.

I as a Co-Author, endorse this level of contribution by the candidate indicated above is appropriate.

James Semmens

Peter O'Leary

Jim Codde

Nerida Steel

Vincent Williams

Paul Cohen

Yee Leung

Katrina Spilsbury

Victoria Westoby

Heidi Pavicic

Appendix 2: Human Research Ethics Approvals

Memorandum

To	Professor James Semmens, Centre for Population Health Research,
From	Professor Stephan Millett, Chair, Human Research Ethics Committee
Subject	Protocol Approval **HR 86/2012**
Date	7 September 2012
Copy	Ms Aime Munro, School of Biomedical Science, Associate Professor Vincent Williams, School of Biomedical Science

Thank you for your application (4308) submitted to the Human Research Ethics Committee (HREC) for the project titled *"Evaluation of the trends and outcomes for women screened for and diagnosed with precursor lesions or cervical carcinoma: A Western Australian perspective utilising data linkage"*. Your application has been reviewed by the HREC and is **approved**.

- You have ethics clearance to undertake the research as stated in your proposal.
- The approval number for your project is **HR 86/2012**. *Please quote this number in any future correspondence.*
- Approval of this project is for a period of twelve months **04-09-2012** to **04-09-2013**. To renew this approval a completed Form B (attached) must be submitted before the expiry date **04-09-2013**.
- Your project has the following special condition:
  1. Please provide a letter of consent from the CEO of WA Cervical Cytology Register to access the CCR Database.

  It is your responsibility, as the researcher, to meet the condition outlined above and to retain the necessary records demonstrating that this has been completed.

Applicants should note the following:

It is the policy of the HREC to conduct random audits on a percentage of approved projects. These audits may be conducted at any time after the project starts. In cases where the HREC considers that there may be a risk of adverse events, or where participants may be especially vulnerable, the HREC may request the chief investigator to provide an outcomes report, including information on follow-up of participants.

The attached **FORM B** should be completed and returned to the Secretary, HREC, C/- Office of Research & Development:
When the project has finished, or
- If at any time during the twelve months changes/amendments occur, or
- If a serious or unexpected adverse event occurs, or
- 14 days prior to the expiry date if renewal is required.
- An application for renewal may be made with a Form B three years running, after which a new application form (Form A), providing comprehensive details, must be submitted.

Yours sincerely,

Professor Stephan Millett
Chair Human Research Ethics Committee

Standard conditions of ethics approval

These standard conditions apply to all research approved by the Curtin University Human Research Ethics Committee. It is the responsibility of each researcher named on the application to ensure these conditions are met.

1. **Compliance.** Conduct your research in accordance with the application as it has been approved and keep appropriate records.
   a. If you are a Higher Degree by Research student, data collection must not begin before your Application for Candidacy is approved by your Faculty Graduate Studies Committee.
2. **Adverse events.** Consider what might constitute an adverse event and what actions may be needed if an adverse event occurs. Follow the procedures for reporting and addressing adverse events (http://research.curtin.edu.au/guides/adverse.cfm).Where appropriate, provide an adverse events protocol. The following are examples of adverse events:
   a. Complaints
   b. Harm to participants. This includes physical, emotional, psychological, economic, legal, social and cultural harm (NS Section 2)
   c. Loss of data or breaches of data security
   d. Legal challenges to the research
3. **Standard forms.** Use the standard forms for the following
   a. **Monitoring.** Assist the Committee to monitor the conduct of the approved research by completing promptly and returning all project review forms that are sent to you.
   b. **Annual report.** Submit an annual report on or before the anniversary of the approval.
   c. **Extensions.** If you are likely to need more time to conduct your research than is already approved, complete an application for extension four weeks before the current approval expires.
   d. **Changes to protocol.** Any changes to the protocol are to be approved by the Committee before being implemented.
   e. **Changes to researcher details.** Advise the Committee of any changes in the details of researchers involved in the approved study.
   f. **Discontinuation.** You must inform the Committee, giving reasons, if the research is not conducted or is discontinued before the expected completion date.
   g. **Closure.** Submit a final report when the research is completed. Include details of when data are to be destroyed, and how, or if any future use is planned for the data
4. **Data management plan.** Have a Data Management Plan consistent with the University's recordkeeping policy. This will include such things as how the data are to be stored, for how long, and who has authorised access.
5. **Publication.** Where practicable, ensure the results of the research are made available to participants in a way that is timely and clear (NS 1.5). Unless prohibited from doing so by contractual obligations, ensure the results of the research are published in a manner that will allow public scrutiny (NS 1.3, d). Inform the Committee of any constraints on publication.
6. **Police checks and other clearances.** All necessary clearances, such as Working with Children Checks, first aid certificates and vaccination certificates, must be obtained before entering a site to conduct research.
7. **Participant information.** All information for participants must be approved by the HREC before being given to the participants or made available to the public.
   a. **University logo.** All participant information and consent forms must contain the Curtin University logo and University contact details for the researchers. Private contact details should not be used.
   b. **Standard statement.** All participant information forms must contain the HREC standard statement.

   This study has been approved by the Curtin University Human Research Ethics Committee (Approval Number HR 86/2012). The Committee is comprised of members of the public, academics, lawyers, doctors and pastoral carers. If needed, verification of approval can be obtained either by writing to the Curtin University Human Research Ethics Committee, c/- Office of Research and Development, Curtin University, GPO Box U1987, Perth, 6845 or by telephoning 9266 2784 or by emailing hrec@curtin.edu.au.

   c. **Plain language.** All participant information must be in plain language that will be easily understood by the participants.

Please direct all communication through the Research Ethics Office

HUMAN RESEARCH ETHICS COMMITTEE (DOHWA HREC) AHEC EC00422

Postal Address:
Executive Officer
DOHWA HREC
1st Floor 'C' Block
189 Royal Street
EAST PERTH WA 6004

ph: (08) 9222 4278
fax: (08) 9222 4236
e-mail: HREC@health.wa.gov.au
http://www.health.wa.gov.au/healthdata/hrec/

Prof James Semmens
Curtin Health Innovation Research Institute, CHIRI
Curtin University
GPO Box U1987
PERTH WA 6845

Project #2012/49

Evaluation of the Trends and Outcomes for Women Screened for an Diagnosed with Precursor Lesions or Cervical Carcinoma: A Western Australian Perspective Utilising Data Linkage

Date of commencement:	01/09/2012		
Date of completion:	31/12/2014		
Research team:	Prof James Semmens	A/Prof Vincent Williams	Dr Jim Codde
	Prof Peter O'Leary	Dr Katrina Spilsbury	Prof Yee Leung
	Nerida Steel	Jacek Gonsalves	Aime Munro
DOH data required:	Yes		
Data linkage required:	Yes		
Datasets to be accessed:	WA Cancer Register;	Mortality;	
	Hospital Morbidity;	WA Cervical Cytology Registry.	
Ethics approval validity:	valid to: 31/10/2016		

I am pleased to advise that the Committee has granted ethical approval for this project.

This letter constitutes Ethics Approval only; you will not receive the data requested for your project until approval for the release of these data is signed by the Department of Health WA Director General's delegate.

This approval is subject to your continued compliance with the following conditions:

* DOHWA HREC holds the Principal Investigator responsible for the ethical conduct of the project and the security of the personal health information therefore he/she must -
  1. Report anything which might warrant review of ethical approval of the project in the specified format including:
     * Any serious or unexpected adverse events; and
       Unforeseen events that might affect the continued ethical acceptability of the project.
  2. Submit for approval any changes or amendments to the research protocol, including methodology, data required, duration of the project and any changes to the approved data storage arrangements.
  3. Advise if the project is discontinued or withdrawn before the expected date of completion and give reasons for this action.
  4. Provide an annual progress report to the HREC and a final report at the completion of the project.

5. Advise any changes of personnel in the research team, and provide a DOHWA Confidentiality Agreement/Confidentiality Acknowledgement form for any addition to the research team.

We wish you well with your project.

Yours sincerely

A/Prof Judith Allen
Chair
Department of Health WA Human Research Ethics Committee

3 October 2012

Appendix 3: Cervical Screening Registry of WA Cytology Codification Sheet

Cytology Codes (WA)
For Use by the Cervical Cytology Registry

Government of Western Australia
Department of Health
WA Cervical Cancer Prevention Program

National Cervical Screening Program
A joint Australian, State and Territory Government Initiative

SPECIMEN

A TYPE	AØ Not stated	A1 Conventional smear	A2 Liquid based specimen	A3 Conventional and liquid based specimen

B SITE	BØ Not stated	B1 Cervical	B2 Vaginal	B3 Other gynaecological site

CYTOLOGY

C CATEGORY	S SQUAMOUS CELL		E ENDOCERVICAL		O OTHER/NON-CERVICAL	
CU Unsatisfactory	SU	Unsatisfactory for evaluation e.g. poor cellularity, poor preservation, cell detail obscured by inflammation/blood/ degenerate cells	EU	Due to the unsatisfactory nature of the smear, no assessment has been made	OU	Due to the unsatisfactory nature of the smear, no assessment has been made
C1 Normal	S1	Cell numbers and preservation satisfactory. No abnormality or only reactive changes	E-	Not applicable: vault smear/previous hysterectomy	O1	No other abnormal cells
			EØ	No endocervical component		
			E1	Endocervical component present. No abnormality or only reactive changes		
C2 Possible LGEA/LGEA	S2	Possible low-grade squamous intraepithelial lesion (LSIL)	E2	Atypical endocervical cells of uncertain significance	O2	Atypical endometrial cells of uncertain significance
	S3	Low-grade LSIL (HPV and/ or CIN I)			O3	Atypical glandular cells of uncertain significance—site unknown
C3 Possible HGEA	S4	Possible high-grade squamous intraepithelial lesion (HSIL)	E3	Possible high-grade endocervical glandular lesion	O4	Possible endometrial adenocarcinoma
					O5	Possible high-grade lesion—non-cervical
C4 HGEA	S5	High-grade squamous intraepithelial lesion (HSIL) (CIN II/ CIN III)	E4	Adenocarcinoma-in-situ		
	S6	High-grade squamous intraepithelial lesion (HSIL) with possible microinvasion/invasion	E5	Adenocarcinoma-in-situ with possible microinvasion/ invasion		
C5 Malignant	S7	Squamous carcinoma	E6	Adenocarcinoma	O6	Malignant cells—uterine body
					O7	Malignant cells—vagina
					O8	Malignant cells—ovary
					O9	Malignant cells—other

RECOMMEND

RØ No recommendation	R4 Repeat smear 6 months	R8 Referral to specialist
R1 Repeat smear 3 years	R5 Repeat smear 6–12 weeks	R9 Other management recommended
R2 Repeat smear 2 years	R6 Colposcopy/ biopsy recommended	RS Symptomatic—clinical management required
R3 Repeat smear 12 months	R7 Already under gynaecological management	

Edition Date: June 2012

90

Appendix 4: Cervical Screening Registry of WA Histology Codification Sheet

Cytology Codes (WA)
For Use by the Cervical Cytology Registry

Government of Western Australia
Department of Health
WA Cervical Cancer Prevention Program

National Cervical Screening Program
A joint Australian, State and Territory Government Initiative

SPECIMEN

A TYPE	AØ Not stated	A1 Conventional smear	A2 Liquid based specimen	A3 Conventional and liquid based specimen

B SITE	BØ Not stated	B1 Cervical	B2 Vaginal	B3 Other gynaecological site

CYTOLOGY

C CATEGORY	S	SQUAMOUS CELL	E	ENDOCERVICAL	O	OTHER/NON-CERVICAL
CU Unsatisfactory	SU	Unsatisfactory for evaluation e.g. poor cellularity, poor preservation, cell detail obscured by inflammation/blood/ degenerate cells	EU	Due to the unsatisfactory nature of the smear, no assessment has been made	OU	Due to the unsatisfactory nature of the smear, no assessment has been made
C1 Normal	S1	Cell numbers and preservation satisfactory. No abnormality or only reactive changes	E- / EØ / E1	Not applicable: vault smear/previous hysterectomy / No endocervical component / Endocervical component present. No abnormality or only reactive changes	O1	No other abnormal cells
C2 Possible LGEA/LGEA	S2 / S3	Possible low-grade squamous intraepithelial lesion (LSIL) / Low-grade LSIL (HPV and/ or CIN I)	E2	Atypical endocervical cells of uncertain significance	O2 / O3	Atypical endometrial cells of uncertain significance / Atypical glandular cells of uncertain significance—site unknown
C3 Possible HGEA	S4	Possible high-grade squamous intraepithelial lesion (HSIL)	E3	Possible high-grade endocervical glandular lesion	O4 / O5	Possible endometrial adenocarcinoma / Possible high-grade lesion—non-cervical
C4 HGEA	S5 / S6	High-grade squamous intraepithelial lesion (HSIL) (CIN II/ CIN III) / High-grade squamous intraepithelial lesion (HSIL) with possible microinvasion/invasion	E4 / E5	Adenocarcinoma-in-situ / Adenocarcinoma-in-situ with possible microinvasion/ invasion		
C5 Malignant	S7	Squamous carcinoma	E6	Adenocarcinoma	O6 / O7 / O8 / O9	Malignant cells—uterine body / Malignant cells—vagina / Malignant cells—ovary / Malignant cells—other

RECOMMEND

RØ No recommendation	R4 Repeat smear 6 months	R8 Referral to specialist
R1 Repeat smear 3 years	R5 Repeat smear 6–12 weeks	R9 Other management recommended
R2 Repeat smear 2 years	R6 Colposcopy/ biopsy recommended	RS Symptomatic—clinical management required
R3 Repeat smear 12 months	R7 Already under gynaecological management	

Edition Date: June 2012

HP003308 JUNE'12

Appendix 5: Survey sent to Western Australian General Practitioners

Partners in ensuring success of the National Cervical Screening Program

Demographic information

1. Please enter your practice postcode

[   ]

2. What is your gender?

○ Female

○ Male

3. What is your age?

○ < 35 years

○ 35-44 years

○ 45-54 years

○ > 55 years

4. How many years have you been practising as a general practitioner?

○ < 2 years

○ 2-5 years

○ 6-10 years

○ 11-19 years

○ 20+ years

5. How many direct patient hours do you work per week?

○ < 10 hours

○ 11-20 hours

○ 21-40 hours

○ 41-60 hours

○ > 61 hours

6. Is your general practice registered to claim the Practice Incentive Program for cervical screening?

○ Yes

○ No

○ Unsure

7. Does your practice employ nurses or midwives who are able to perform Pap smears?

○ Yes

○ No

25%
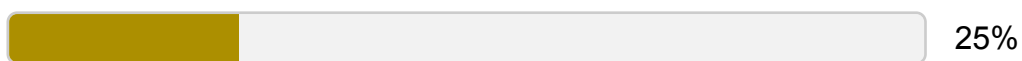
Next

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The following journals provided the Authors with rights to include their journal articles in their thesis:

- *Australian Family Physician*
- *Gynecological Oncology*

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AFP
Australian Family Physician

29 January 2015

RE: PERMISSION REQUEST

Dear Aime Munro,

Thank you for your request for permission to include material originally published in *Australian Family Physician* (AFP) for your PhD thesis.

The RACGP is happy to grant you permission to include the AFP articles:

Munro A, Codde J, Semmens J, et al. Utilisation of co-testing (human papillo-mavirus DNA testing and cervical cytology) after treatment of CIN: a survey of GPs' awareness and knowledge. Aust Fam Physician 2015;44(1):64–68. Available at www.racgp.org.au/afp/2015/januaryfebruary/utilisation-of-co-testing-%28human-papillomavirus-dna-testing-and-cervical-cytology%29-after-treatment-of-cin-a-survey-of-gps%E2%80%99-awareness-and-knowledge

Munro A, Pavicic H, Leung Y, et al. The role of general practitioners in the continued success of the National Cervical Screening Program. Aust Fam Physician 2014;43(5):293–96. Available at www.racgp.org.au/afp/2014/may/national-cervical-screening-program

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Journalist, Good Practice
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Total	0.00 AUD

Additional material 1: WA Cervical Cancer Prevention Program's website development
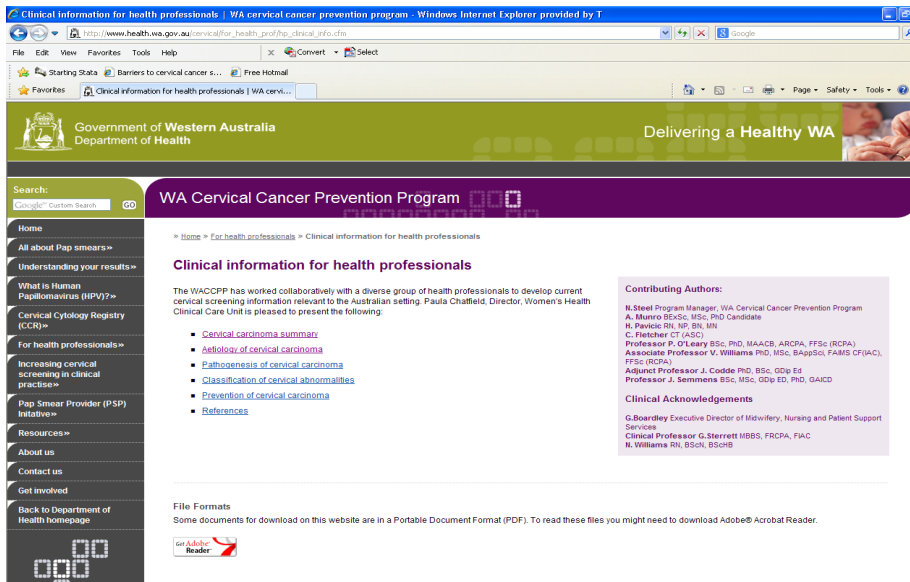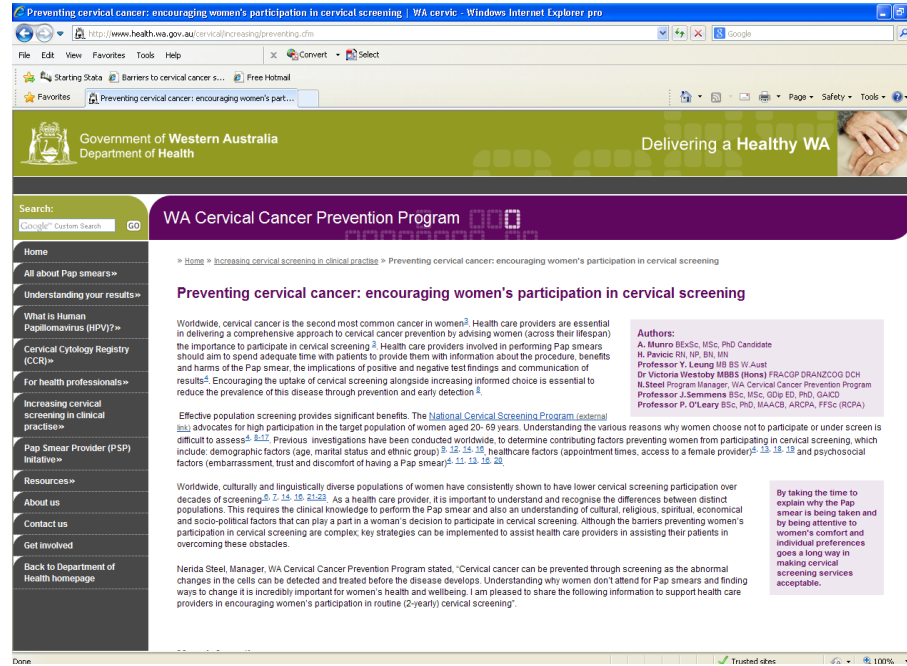
Additional material 2: Nursing and midwives toolkit

Cervical Cancer Prevention Tool Kit for Australian Nurses and Midwives

By Heidi Pavicic, Aime Munro, Nerida Steel and Natalie Williams

Cervical cancer is a worldwide health issue and one of the most preventable of all cancers (World Health Organization [WHO] 2013). Australia adopts an organised approach to cervical screening and encourages women's participation in cervical screening to detect abnormal cell changes in the cervix, which if left undetected and untreated may progress to cervical cancer (National Cervical Screening Program [NCSP] 2011). In Australia, 631 new cases of cervical cancer were diagnosed in 2009 and 152 women died from the disease in 2010 (Australian Institute of Health and Welfare [AIHW] 2013). All women who are sexually active are at risk of human papillomavirus (HPV) infection; it is estimated 75% will involve an oncogenic HPV type (Peto et al 2004). Throughout Australia in 2011, eight out of every 1,000 women screened had a histologically confirmed high-grade cervical abnormality, providing an opportunity to treat women before possible progression to cancer (AIHW 2013).

Nurses and midwives are well placed to provide cervical screening services, as they can identify and support each woman's right to have access to complete information and actively encourage women to participate in all aspects of their health care (WA Cervical Cancer Prevention Program 2013; Queensland Cervical Screening Program 2012). Through collaboration with, and support of, Australian nurses and midwives we can increase women's access to safe and culturally appropriate cervical screening services. To support the delivery of high quality services, nurses and midwives have the opportunity to undertake appropriate education and training and, if available, to credential as a Pap smear provider. The credentialling of nurses and midwives as Pap smear providers is demonstration of an ongoing commitment to deliver high quality provision of Pap smears throughout Australia (WA Cervical Cancer Prevention Program 2013; Queensland Cervical Screening Program 2012). Further information related to education and credentialling as a nurse/midwife Pap smear provider may be obtained by contacting your local cervical cytology ('Pap smear') registry or local cervical cancer prevention program.

As a Pap smear provider you are responsible for supporting each individual woman throughout the screening pathway, from recruitment through to diagnosis (WA Cervical Cancer Prevention Program 2013; Queensland Cervical Screening Program 2012). A Pap smear may be a personally challenging procedure for a woman; therefore, it is important to ensure women participating in cervical screening are both psychologically and physically comfortable throughout the examination (WA Cervical Cancer Prevention Program 2013; Queensland Cervical Screening Program 2012; Stewart and Thistlethwaite 2010).

National competency standards for Pap smear providers

As a Pap smear provider you are required to adhere to and uphold the *National Standards for Nurse Pap Smear Providers*. These standards relate to the legal and ethical responsibilities for Pap smear providers, and include:

- Demonstrates accurate knowledge for safe practice.
- Protects the rights of individuals.
- Recognises own ability and level of professional competence.
- Acts to enhance the dignity and integrity of women.
- Maintains a physical and psycho-social environment which promotes safety, security and optimal health care.
- Acts to maintain the right of women to make informed decisions.
- Integrates comprehensive health assessment and interpretive skills to achieve optimal care for women.
- Collaborates with the health care team to achieve desired outcomes.

How do you assess who needs a Pap smear?

The NCSP recommends all women aged 18 to 69 years, who have ever been sexually active, whether vaccinated or not, participate in two-yearly cervical screening (NCSP 2011). This policy applies only to asymptomatic women. Symptomatic women require referral and further investigation. The policy states (NCSP 2011):

- All women with an intact cervix who have ever been sexually active (any genital-skin to genital-skin contact) should commence having Pap smears between the ages of 18 and 20 years, or one to two years after sexual debut, whichever is *later*.
- Women who have had a hysterectomy may cease having Pap smears, providing their hysterectomy included removal of the cervix and was performed for benign reasons.
- Pap smears may cease at the age of 70 years for women who have had two normal Pap smears within the past five years. Women 70 years and over that have never had a Pap smear, or who request a Pap smear, should be screened.
- Women with a past history of high-grade cervical lesions, or who are being followed-up for previous abnormal smears should be clinically managed in accordance with the National Health and Medical Research Council (NHMRC) guidelines *Screening to prevent cervical cancer: guidelines for the management of asymptomatic women with screen detected abnormalities* (2005).

How do you assess women for their Pap smear?

First, a thorough medical, gynaecological and obstetrical history needs to be obtained, particularly enquiring about any:

- postmenopausal bleeding (PMB) or spotting;
- postcoital bleeding (PCB) or spotting;
- intermenstrual bleeding (IMB) or spotting; and
- abnormal vaginal discharge.

If any of these symptoms are present, a Pap smear should be taken and the woman should be immediately referred to a medical

practitioner. A thorough history will also assist in determining the need for opportunistic testing for sexually transmitted infections.

Key factors for a positive patient experience

Pap smear providers should seek feedback from their patients as part of their quality assurance measures to ensure a positive Pap smear experience occurs for the woman. Positive outcomes for the woman may include (WA Cervical Cancer Prevention Program 2013; Queensland Cervical Screening Program 2012):

- Equipping the woman with information to support her decision to have a Pap smear.
- Creating a safe and supportive environment where a woman can ask sensitive questions.
- Establishing a plan to communicate the Pap smear results to the woman.
- Taking the time to alleviate anxiety and ensure understanding of what the Pap smear results mean.
- The roles and benefits of cervical cytology registries are explained to the woman.
- The woman knows when her next Pap smear is due.

The human papillomavirus

Human papillomavirus (HPV) is a common sexually transmitted infection with approximately four out of five women being infected at some point throughout their lifetime (Castellsague et al 2009; Castellsague 2008; Bosch and de Sanjose 2003). Studies have identified approximately 99.7% of cervical cancers are positive for HPV DNA (Wallboomers et al 1999). Transference of HPV to the genital region primarily occurs through genital-skin to genital-skin contact (Rodriguez et al 2010). The majority of HPV infections are cleared by the woman's body within one to two years (Rodriguez et al 2010), with approximately 50% of HPV infections spontaneously clearing within eight months of initial infection and 90% being cleared within two years (Moscicki et al 2006). There are more than 100 types of HPV, with 40 types affecting the genital region. Among the genital HPV infections, there are both low-risk (LR) HPV and high-risk (HR) HPV types. LR HPV is non-cancer causing and often presents as genital warts, with types 6 and 11 causing 90% of these cases (Munoz et al

2003). HR HPV is recognised as a necessary, although not sufficient, cause of virtually all cervical cancer cases (Bosch et al 2002; Bosch et al 2006; Castle et al 2005). HR HPV types 16 and 18 alone are responsible for 70% of cervical cancer cases (Bosch et al 2008). The progression from HPV infection to cervical cancer may take up to five to 15 years (Castellsagué et al 2009); however, the majority of HR HPV infections do not progress to cervical cancer as the body is often able to clear this infection (Castellsagué et al 2009; Burd 2003).

Tips for explaining HPV infection to women

- Most sexually active women (four out of five) will have this virus at some point in their lives.
- Most women clear the virus on their own within two years.
- Over 100 types of this virus exist.
- 40 types of HPV can affect the genital region, of these there exist low-risk and high-risk HPV types.
- Low-risk HPV types are non-cancer causing and often cause genital warts.
- High-risk HPV types *may* cause cancer, *if* the body does not clear the virus.
- High-risk HPV types 16 and 18 cause over 70% of cervical cancer.
- Timeline from getting HPV to cervical cancer *may* take up to five to 15 years.

Cervical cancer prevention
Primary prevention: HPV vaccines

HPV vaccination is a primary prevention intervention and protects against HR HPV types 16 and 18 that cause 70% of all cases of cervical cancer (Brotherton 2008; Harper et al 2006; Villa et al 2005). HPV vaccination has been approved in over 100 countries, as the vaccines are both safe and efficacious (Koutsky and Harper 2006). In Australia two types of HPV vaccines have been approved for use, Gardasil® and Cervarix® (Szarewski 2012; Brotherton et al 2011). Since 2007 Gardasil® has been included in the Australian school-based vaccination program, which includes the vaccination of girls aged 12 to 13 years, at no cost to the individual (Australian Government Department of Health and Ageing 2006). Gardasil® is administered as an intramuscular injection (IM), given in three doses with the initial dose, then at two and six months (CSL

Limited 2013). Potential side effects may include allergic reactions, injection site reactions, headaches, fever, nausea and dizziness (CSL Limited 2013). Contraindications to Gardasil® include hypersensitivity or severe allergy to yeast, prior allergic reaction to Gardasil® and pregnancy (CSL Limited 2013).

It is important to note HPV vaccines are not a therapeutic vaccine, rather they are designed to prevent initial HPV infection (Brotherton et al 2011; Harper et al 2006; Villa et al 2005), therefore the vaccine is most effective if all three doses are administered to females prior to the commencement of sexual activity (Brotherton et al 2011; Harper et al 2006; Villa et al 2005). Whilst the advisement by HPV vaccination guidelines is to vaccinate young girls before their sexual debut, natural history studies indicate that all sexually active women may benefit from the vaccination (Brotherton 2008; Ault 2007; Harper et al 2006; Villa et al 2005). Should the girl or woman have already initiated sexual activity she may still be offered vaccination after a discussion about the risks and benefits to assist her in making an informed decision (Castellsagué et al 2009). Health care providers should educate the woman of the benefits of vaccination combined with the importance of continued cervical screening (Castellsagué et al 2009).

Secondary prevention: cervical screening

Australia's cervical screening program operates as a joint program of the Australian government and state and territory governments, with a target group of women aged 18-69 years (NCSP 2011). The primary cervical screening tool used in Australia, is the Pap smear, or 'Pap test'. Pap smears enable identification of early cellular changes in the cervix, which if left undetected and untreated may progress to cervical cancer (AIHW 2013). Pap smears have been proven to prevent 70% of cases of squamous cell carcinoma (AIHW 2013) and thus, promotion of regular cervical screening to all eligible female patients is crucial. Over 50% of women who develop cervical cancer have never had a Pap smear, have been screened irregularly, or have not been screened within the previous five years (Coleman and Poznansky 2006).

Cervical Cancer Prevention Tool Kit for Australian Nurses and Midwives

2

31

CLINICAL UPDATE

Cervical Cancer Prevention Tool Kit for Australian Nurses and Midwives

Tips for explaining cervical cancer prevention to women

- HPV vaccination offers protection against HR HPV types 16 and 18, which cause 70% of cervical cancers.
- In Australia there are two types of HPV vaccines, Gardasil® and Cervarix®, which protect against HPV types 16 and 18.
- Gardasil® is free for girls aged 12 to 13 years, as part of the school-based vaccination program.
- HPV vaccination does not protect against all cancer causing types of HPV and therefore vaccinated women still need to have regular Pap smears.

- Pap smears are looking for any cervical cell changes, which if found early, can be managed and possibly treated if required, before progression to cervical cancer.

How do you manage pregnant women?

Pregnancy is a time when women often have the greatest interest in their health and thus are likely to participate in cervical screening, should it be offered. Offering cervical screening to pregnant women is essential as 1-3% of women diagnosed with cervical cancer are pregnant or postpartum at the time of cancer diagnosis (Nguyen et al 2005; Creasman 2001). Approximately 50% of these cases are diagnosed prenatally and the other half is diagnosed within 12 months of the delivery (Smith et al 2001). As a Pap smear provider you may be able to promote opportunistic screening at the patient's booking visit or, if more appropriate for the woman, at the follow-up visit.

The Royal Australian and New Zealand College of Obstetricians and Gynaecologists advises a Pap smear should be offered to every asymptomatic pregnant woman who is due for cervical screening (NCSP 2011). Ideally screening would occur prior to the third trimester; however, screening is safe beyond this gestation (NCSP 2011). Symptomatic pregnant women are managed the same as non-pregnant women, with a requirement of referral and further investigation (NCSP 2011). Pregnant women with abnormal smear results should be managed in accordance with the NHMRC guidelines (NCSP 2011).

How do you manage patients with screen detected abnormalities?

Patients who may require specific clinical management outside the 2005 NHMRC guidelines include those who present with symptoms such as:

- intermenstrual bleeding or spotting;
- postcoital bleeding or spotting; and
- postmenopausal bleeding or spotting.

Patients with any of the above symptoms or any other signs or symptoms of concern should be immediately referred for further tests so that their condition can be clinically assessed and an appropriate management plan formulated (NCSP 2011).

The Pap smear provider must have an awareness of health care agencies and community resources available to women for follow-up care and treatment of cervical abnormalities (Queensland Cervical Screening Program 2012). A diverse range of health care providers and resources available within the immediate locality need to be provided to the woman so that she has a range of options for her follow-up and treatment plan. All steps taken to encourage the woman to attend for follow-up should be clearly documented in the woman's record. For medico-legal

Pap smear result	Clinical interpretation	Communication to woman
Unsatisfactory Pap smear	The laboratory report should state why the Pap smear was unsatisfactory, which may include reasons such as: • the cells may be obscured by blood or inflammation/mucous; • there may not be enough cells on the sample to give an accurate assessment; • the cells may be atrophic and difficult to interpret; • the smear may not have been properly prepared or the slide may have broken during transit to the laboratory.	When providing the results to the woman ensure that she clearly understands: • The unsatisfactory result does not indicate cancer; • The laboratory was unable to get a clear reading and is therefore unable to provide a result; • A repeat Pap smear is required within three months
Negative Pap smear	A negative Pap smear result for asymptomatic women who have no history suggestive of cervical pathology means their test result was normal. • Recommendation of repeat Pap smear in two years.	• Pap smear result was normal. • All the cells seen were normal. • Repeat Pap smear in two years.
Possible or definite low-grade squamous intraepithelial lesion (LSIL)	This result indicates minor squamous cell changes that are often due to an acute infection with human papillomavirus (HPV). A woman with a Pap smear report of LSIL should be managed in the same manner, irrespective of whether the cervical abnormality is reported as possible or definite LSIL, and offered a repeat Pap smear in 12 months. Note: Women aged 30 years or more with a possible or definite LSIL, without a negative Pap smear history in the preceding two to three years are managed differently. These cohorts of women need to have an immediate colposcopy or a repeat Pap smear within six months.	• This result means that the cells seen are a little bit different. This is not a diagnosis of cancer. • The cells are a little bit different because of an HPV infection. • The body will normally clear the infection by itself in one to two years. • A repeat Pap smear is needed in 12 months to check the cells again and ensure the body has cleared the infection.
Possible or definite high-grade squamous intraepithelial lesion (HSIL)	Women with a possible or definite HSIL should be referred to a gynaecologist for colposcopic assessment and targeted biopsy. This result represents suspected or definite changes commonly associated with a persistent HPV infection which, if left untreated, may progress to cervical cancer.	• This result means that the cervical cells are different and need to be looked at carefully. This does not mean a diagnosis of cancer. • This result means that there is a lasting HPV infection that may require treatment. • You will be referred to a specialist who can look at your cervix and work out if treatment is needed.
Cervical glandular abnormalities	A Pap smear result reporting: • adenocarcinoma; • endocervical adenocarcinoma in situ; • possible high-grade glandular lesion; • atypical endocervical cells; • endocervical cells of undetermined significance. Should be referred as soon as possible to a gynaecologist with expertise in colposcopic evaluation of suspected glandular malignancies, or a gynaecological oncologist.	• Glandular cells are located inside the cervix. • These cells are harder to locate and look at. • For these reasons you need to be seen by a specialist who can have a better look at these cell changes and provide treatment.

reasons, the Pap smear provider must keep documented evidence of all correspondence relating to the follow-up of abnormal results.

Conclusion

Nurses and midwives that provide women's health services, including the provision of Pap smears, are well placed to encourage women's participation in cervical screening. Through collaboration, Australian nurses and midwives can actively contribute to decreasing morbidity and mortality from this largely preventable disease. Together, nursing and midwifery health care providers can increase women's access to safe and culturally appropriate cervical screening services throughout Australia.

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CLINICAL UPDATE

Cervical Cancer Prevention Tool Kit for Australian Nurses and Midwives

4

33

Additional material 3: Western Australian Pap Smear Provider Synopsis

Cervical screening: synopsis for WA Pap smear providers

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March 2013

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Clinical acknowledgements

Foreword

The WA Cervical Cancer Prevention Program (WACCPP) was established in 1992 as part of the National Cervical Screening Program and is one of the six programs that reside within the Women's Health Clinical Care Unit (WHCCU) in the Women and Newborn Health Service. The WACCPP is committed to increasing the number of credentialed nurses and midwives as Pap smear providers to deliver cervical screening services throughout Western Australia. Pap smear providers play a critical role in women's health as they:

- enhance and complement existing cervical screening services
- ensure that Western Australian women have access to high quality cervical screening services
- increase women's access to female health care providers (as the majority of nurses and midwives are female
- assist women in overcoming barriers that prevent them from participating in regular cervical screening
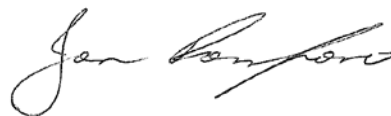
The cervical screening synopsis was developed with valuable input from women's health care providers and professional organisations in WA and was endorsed by the WACCPP in 2013. The purpose of this document is to:

- support health care providers in their delivery of cervical screening services
- guide clinical practice in accordance with the National Health and Medical Research Council guidelines *Screening to Prevent Cervical Cancer: Guidelines for the Management of Asymptomatic Women with Screen Detected Abnormalities*
- promote best practice standards
- be used as a quality assurance reference

The WHCCU adopts a holistic approach to promote the health and wellbeing of WA women. Through collaborative relationships we strive to improve women's health, particularly for vulnerable women who are at most risk for cervical abnormalities. We hope that the distribution and use of this document will assist the WACCPP in reaching these goals.

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Women's Health Clinical Care Unit
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Assoc Prof Jonathan Rampono
Chair
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Contents

1. Executive summary

Cervical cancer is a worldwide health issue and is one of the most preventable of all cancers. Since the introduction of the Papanicolaou (Pap) smear as a cervical screening tool, up to 90% of squamous cell carcinomas have been prevented. Human papillomavirus (HPV) infection is well-established as the principal cause of 99.7% of cervical cancer cases. There are many different subtypes of HPV that can infect the anogenital tract, but two HPV subtypes known as type 16 and 18 are responsible for 70% of all cervical cancer cases worldwide. HPV vaccines that prevent HPV type 16 and 18 infections are now available and have the potential to reduce the incidence of cervical and other anogenital cancers.

In 1991, the Australian Government accepted recommendations made by the Screening Evaluation Steering Committee to the Australian Health Ministers' Advisory Council (AHMAC) and implemented the Organised Approach to Preventing Cancer of the Cervix, now known as the National Cervical Screening Program (NCSP). The NCSP operates as a joint program of the Australian, and state and territory governments. The Australian cervical screening program recommends a 2-yearly screening interval for asymptomatic women, has adopted standardised quality assurance guidelines for the management of screen detected abnormalities and established Pap smear registries in every state and territory.

The WA Cervical Cancer Prevention Program (WACCPP) is the State funded component of the NCSP, and is responsible for the management and operation of the statewide cervical screening program. The WACCPP aims to reduce the incidence and mortality attributable to cervical cancer. The Program achieves this through support of existing health care systems and the implementation of appropriate strategies to enhance women's participation in cervical screening.

2. Aetiology of cervical cancer

The National Institute of Health Consensus Conference on cervical cancer stated, "cervical carcinoma is the first solid tumour to be shown to be virally induced in essentially every case." Results from a large international collection of cervical tumour specimens have identified the human papillomavirus (HPV) DNA to be present in 99.7% of all cases[1]. There are more than 100 types of HPV, with 40 types affecting the anogenital region. Among the anogenital HPV infections, there are both low risk (LR) HPV and high risk (HR) HPV types. LR HPV is non-oncogenic and often causes genital warts, with types 6 and 11 causing 90% of these incidences[2]. It is well recognised that infection with HR HPV oncogenic types is a necessary, although not sufficient cause of virtually all cervical cancer cases[3-8]. HR HPV types 16 and 18 alone are responsible for 70% of cervical cancer incidences[9].

In Australia, 637 incidences of cervical cancer were diagnosed in 2008 and 131 women died from this in 2007[10]. This is approximately 9 new cases and 2 deaths per 100,000 women, respectively[10]. In 2010, for every 1,000 women screened, 9 women had a histologically confirmed high-grade cervical abnormality, providing health care providers an opportunity to treat women before possible progression to cancer[10].

There are two main types of cervical cancer, namely squamous cell carcinoma (SCC) and adenocarcinoma[10, 11]. SCC arises in cells in the ectocervix, with the majority of cases being detected in the transformation zone (the ectocervix and endocervix junction) (Figure 1)[10, 11]. Adenocarcinoma arises from mucus producing cells adjacent to the transformation zone or in the endocervical canal[11]. Across Australia in 2007 SCC comprised 63.4% of all cervical cancer cases, followed by adenocarcinoma (24.9%), adenosquamous (3.9%) and all other cervical cancers (7.9%)[12].

Figure 1. Female reproductive organs, endocervix, ectocervix and transformation zone.
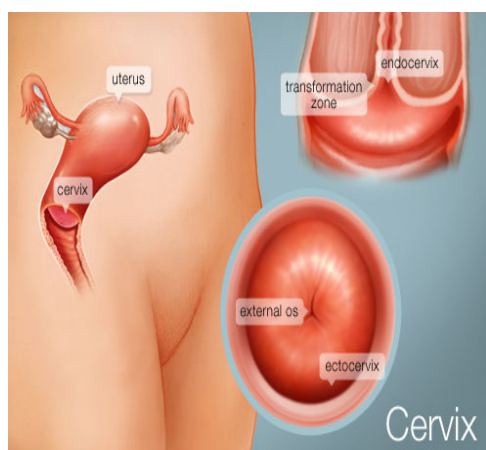
The development of squamous cervical carcinoma is related to both host and viral characteristics such as viral oncogenicity, inadequacy of the patient's immune system response and any associated risk factors which may include[2, 13-16]:

- multiple sexual partners
- a partner with multiple previous or current sexual partners
- young age at first sexual intercourse
- persistent infection with a high risk (HR) HPV type e.g. HPV 16 or HPV 18
- cigarette smoking

There is evidence that cofactors contributing to the progression of adenocarcinoma, including those with HR HPV, are different from those that contribute towards progression to squamous cell carcinoma[17]. Adenocarcinomas have been associated with different associated risk factors such as[17]:

- obesity
- sero-positivity for Herpes simplex virus type 2 (HSV-2)
- endogenous hormonal factors such as parity and exogenous hormone use such as the oral contraceptive

3. Pathogenesis of cervical cancer

Human papillomavirus infection is a common sexually transmitted infection with approximately 11.4% of the female population estimated to be infected worldwide[13, 18]. Molecular testing has demonstrated that over 99.7% of cervical cancers are positive for HPV DNA[1]. Transmission of HPV to the anogenital region primarily occurs through microabrasions in the epithelium[19]. Most HPV infections are transient regardless of the age of the woman[19], with approximately 50% of HPV infections spontaneously clearing within 8 months of initial infection and 90% being cleared within 2 years[20-22].

All sexually active women are at risk of HPV infection and it is estimated 75% will involve an oncogenic HPV type[23]. Sexual intercourse is the primary route of transmission of genital HPV infection[18] and peak HPV prevalence has been identified soon after the onset of sexual activity in adolescence and early adulthood[16, 24]. The subsequent age-related decrease in prevalence reflects acquisition of immunity and monogamous relationships. The development of cervical cellular changes from the onset of genital HPV infection to the development of cervical carcinoma can take 10–20 years, although it has been reported that in some cases may only take 1–2 years post sexual debut[5, 16, 25].The duration of the HPV infection is related to the HPV type, on average HR HPV infections last longer than infections with LR HPV. Research indicates that there is a causal relationship between HR HPV infection longevity and the likelihood that it will progress towards a precancerous lesion/carcinoma[16, 19, 26-28]. Approximately, 20-30% of women with persistent HR HPV infection (>12 months) will be diagnosed with a high-grade abnormality within 30 months[22, 26].

The progression from HPV infection to cervical cancer may take approximately up to 5-15 years and can be summarised into four key stages: 1) HPV transmission 2) acute HPV infection 3) viral persistence and the development of a precancerous lesion, and 4) invasion through the basement membrane of the epithelium (carcinoma)[16, 29, 30]. Development of malignant lesions occurs through HR HPV DNA integrating into the host genome in infected cells[31]. Once this event occurs there is potential for the integrated viral genes to interfere with the normal mechanisms that control cell proliferation and destruction of "mutant cells" that can result in the proliferation of abnormal cells[31].

4. Prevention of cervical cancer

4.1   Human papillomavirus vaccine

The development of prophylactic vaccines against human papillomavirus (HPV) infections is the most significant recent advancements in the prevention of cervical carcinoma[32, 33]. HPV vaccination offers primary prevention against HR HPV types 16 and 18 that cause 70% of this disease[34-36]. HPV vaccines have been approved for use in over 100 countries, as the vaccine is safe, well tolerated and efficacious[37]. In Australia there are two types of prophylactic vaccines that have been approved for use, namely Gardasil® and Cervarix®[32, 33].

Gardasil®

In June 2006, the Therapeutic Goods Administration (TGA) approved the use of Gardasil® (CSL Biotherapies/Merck & Co. Inc.) in Australia, for females aged 9 to 26 years and males aged 9 to 15 years[38]. Gardasil® is a recombinant, quadrivalent HPV vaccine that prevents infection with genital HPV types 6, 11, 16 and 18[39]. The Australian Government covers the cost of this vaccine for girls aged 12 to 13 years, as part of the school based Immunisation Program[38]. Gardasil® has been reported to be 98% effective at preventing cervical disease and external genital lesions when administered prophylactically to uninfected women (HPV DNA negative and HPV seronegative for relevant types)[36, 40-43]. Gardasil® is administered as an intramuscular injection (IM), given in 3 doses (0, 2 & 6 months)[39]. Side effects may include injection site reactions, headaches, fever, nausea, dizziness and allergic reactions[39]. Contraindications to this vaccine include hypersensitivity or severe allergy to yeast and prior allergic reaction to Gardasil[39].

Cervarix®

The TGA approved the Cervarix® vaccine in May 2007 (GlaxoSmithKline). Cervarix® differs from Gardasil® as it is a recombinant protein particulate bivalent HPV vaccine that prevents infection by HPV types 16 and 18[44]. It is registered for use in females aged 10–45 years[44]; however, the Australian Government does not support the cost of this vaccine. Cervarix® has been administered and tested in clinical trials capturing approximately 40,000 females, and has consistently displayed high levels of efficacy (upwards of 98%) in preventing precancerous lesions due to HPV types 16 and 18[35]. Cervarix® is administered as an IM injection given in 3 doses (0, 1 & 6 months)[44]. The most common side effects include injection site reactions, headaches, gastrointestinal

symptoms, myalgia, arthralgia and allergic reaction[44]. Contraindications to the vaccine include pregnancy and a prior negative reaction to Cervarix®. Its use is cautioned in women who are either allergic to or have a sensitivity to latex[44].

It is important to note that HPV vaccines are designed to prevent initial HPV infection[33, 35, 36]. They are not a therapeutic vaccine, thus, the vaccine is most effective if given to females prior to the commencement of sexual activity[33, 35, 36]. Whilst vaccinating young girls before their sexual debut is consistently advised by current HPV vaccination guidelines, natural history studies indicate that all sexually active women may benefit from the vaccination[34-36, 41]. Research suggests that only women with confirmed current infections by *both* oncogenic HPV vaccine types will not benefit from the vaccination [45]. Health care providers should assist women of all ages to make an informed decision when considering HPV vaccination[45]. Should the woman be over 25 years of age she may still be offered vaccination after a discussion about the risks and benefits to assist her in making an informed decision[45].

Health care providers should emphasise the benefits of vaccination combined with the importance of continued cervical screening[45].

4.2 Cervical screening

Australia's cervical screening program operates as a joint program of the Australian Government and state and territory governments, targeting women aged 20-69 years[12]. The Australian cervical screening program, utilises the systematic application of a validated test to identify asymptomatic individuals in a population who may have cervical abnormalities[46].

In Australia, the Pap smear, or 'Pap test' is used as the primary cervical screening tool. Pap smears identify early cellular changes in the cervix, which if left undetected and untreated may progress to cervical cancer[12]. A Pap smear can be a personally challenging procedure for a woman; therefore, as a Pap smear provider it is important that women participating in cervical screening are both psychologically and physically comfortable throughout the examination[47, 48].

4.3 National Cervical Screening Program Policy

The National Cervical Screening Program (NCSP) recommends that all women aged 18 to 69 years, who have ever been sexually active, whether vaccinated or not, should

participate in 2-yearly cervical screening. This policy applies only to asymptomatic women. Symptomatic women require referral and further investigation. The Policy states[12]:

- All women who have ever been sexually active (any genital-skin to genital-skin contact) should commence having Pap smears between the ages of 18 and 20 years, or one to two years after sexual debut, whichever is *later*.

- Pap smears may cease at the age of 70 years for women who have had two normal Pap smears within the last five years. Women aged 70 years and over who have never had a Pap smear, or who request a Pap smear, should be screened.

- Women with a past history of high-grade cervical lesions, or who are being followed-up for previous abnormal smears should be managed in accordance with the National Health and Medical Research Council (NHMRC) guidelines *Screening to prevent cervical cancer: guidelines for the management of asymptomatic women with screen detected abnormalities* [49].

4.4   National Cervical Screening Program Policy on pregnancy

Pregnancy is a time when women often have the greatest interest in their health and are more likely to participate in cervical screening if it is offered[47, 48]. Opportunistic screening may be undertaken at the booking visit, unless there is a clinical reason, such as bleeding, which would prohibit performing the Pap smear[12]. The Pap smear could then be performed at the follow-up visit.

The Royal Australian and New Zealand College of Obstetricians and Gynaecologists advised the NCSP that a Pap smear should be offered to every well pregnant woman (without symptoms of cervical cancer) who is due for cervical screening[12]. Ideally screening would occur prior to 24 weeks; however, screening is safe beyond this gestation[12]. Symptomatic pregnant women will need referral and further investigation[12].

Pregnant women with abnormal smear results should be managed in accordance with the NHMRC guidelines[49].

5. Classification of cervical abnormalities

The Australian working party, using the Bethesda System as its basis, derived a unique Australian terminology system for squamous and glandular lesions called the Australian Modified Bethesda System (AMBS 2004, Table 1 and Table 2).

Table 1. The Australian Modified Bethesda System (AMBS 2004) for squamous abnormalities[49]

AMBS 2004	Incorporates
Possible low-grade squamous intraepithelial lesion	Non-specific minor squamous cell changes. Changes that suggest, but fall short of, HPV/ cervical intraepithelial neoplasia (CIN) 1
Low-grade squamous intraepithelial lesion (LSIL)	HPV effect, CIN 1
Possible high-grade squamous intraepithelial lesion	Changes that suggest, but fall short of, CIN 2, CIN 3 or squamous cell carcinoma
High-grade squamous intraepithelial lesion (HSIL)	CIN 2, CIN 3
Squamous cell carcinoma	Squamous cell carcinoma

Squamous abnormalities are classified into possible or definite low-grade squamous intraepithelial lesions (LSIL or HPV+/-CIN 1), possible high-grade squamous intraepithelial lesion (where the presence of a high-grade abnormality such as CIN 2, CIN 3 or squamous cell carcinoma cannot be excluded), high-grade squamous intraepithelial lesions (HSIL, CIN 2 or CIN 3) and squamous cell carcinoma. The cervical cytology classification system assists the medical scientist and pathologist to classify the cervical cellular changes to allow appropriate follow-up recommendations and clinical management[49].

The classification of squamous intraepithelial lesions is characterised by abnormal cellular proliferation and maturation, together with nuclear atypia. In LSIL, the changes predominantly occupy the lower third of the epithelium and marked HPV cytopathic effects (koilocytosis) are often seen. In HSIL, the changes inhabit the lower two thirds of the epithelium (CIN 2), or the full thickness of the epithelium (CIN 3), and the nuclei are hyperchromatic and irregular. HSILs are also characterised by detectable high risk (HR) HPV DNA and chromosomal instability[6].

Although adenocarcinoma in situ (AIS) is defined as a preinvasive cervical lesion, natural history studies to confirm its potential to progress are lacking[50]. AIS is much less commonly diagnosed than the corresponding squamous preinvasive lesions[10]. No terminologies of glandular lesions with lower degrees of nuclear atypia have been established due to rarity in biopsies[51-53].

Table 2. AMBS (2004) for glandular abnormalities[49].

AMBS 2004	Incorporates
Atypical endocervical cells of undetermined significance	Non-specific minor cell changes in endocervical cells
Atypical glandular cells of undetermined significance	Non-specific minor cell changes in glandular cells
Possible high-grade glandular lesion	Changes that suggest, but fall short of, AIS or adenocarcinoma
Endocervical adenocarcinoma in situ	Adenocarcinoma in situ
Adenocarcinoma	Adenocarcinoma

6. Credentialing as a Pap smear provider

The WA Cervical Cancer Prevention Program (WACCPP) is responsible for the management and delivery of the Pap Smear Provider Initiative (PSPI). The PSPI encourages and supports nurses and midwives to credential as a Pap smear provider to increase the opportunity for women to access high quality cervical screening services throughout WA, especially in rural and remote areas. The credentialing process exists to support and ensure high-quality delivery of patient care. Credentialing promotes both the autonomy of an individual's practice and the advancement of nursing and midwifery through:

- increasing recognition of Pap smear provider practice by colleagues and other health disciplines

- increasing the public's awareness of Pap smear provider skills and competencies

The process for credentialing includes submission of documentation to the WACCPP in support of these requirements. Further information can be found at http://www.health.wa.gov.au/cervical/healthprof/hp_become.cfm

6.1   Health practitioner registration

Credentialed Pap smear providers are required to be registered with the Nurses and Midwives Board, which is regulated by the Australian Health Practitioner Regulation Agency (AHPRA). AHPRA is responsible for the regulation of registration and accreditation of fourteen health professions across Australia.

For further information on health practitioner registration and accreditation, please visit: www.ahpra.gov.au

6.2   Essential education and training

To be eligible to credential, nurses and midwives need to have completed an educational program deemed appropriate by the WA Pap Smear Provider Credentialing Committee. For further information relating to approved education programs please contact the WACCPP on 13 15 56.

6.3   National competency standards for nurse Pap smear providers

The *National Standards for Nurse Pap Smear Providers* (1997) relate to the legal and ethical responsibilities for Pap smear providers, and includes accountability for clinical services.

The *National Standards for Nurse Pap Smear Providers* comprise eight competencies. These include:

- Demonstrate accurate knowledge for safe practice

- Protects the rights of individuals

- Recognises own ability and level of professional competence

- Acts to enhance the dignity and integrity of women

- Maintains a physical and psycho-social environment which promotes safety, security and optimal health care

- Acts to maintain the right of women to make informed decisions

- Integrates comprehensive health assessment and interpretive skills to achieve optimal care for women

- Collaborates with the health care team to achieve desired outcomes

For further information regarding the national competency standards for nurse Pap smear providers, please refer to Appendix A.

7. Performing a Pap smear

The Pap smear is a procedure in which cells are collected from the cervix, smeared onto a microscope slide, and sent to a pathology laboratory for cytological examination. Worldwide, the Pap smear is currently the most effective test to prevent squamous cervical cancer worldwide. Correct sampling technique increases the accuracy and adequacy of the smear sample, and decreases the risk of a false negative result[54].

7.1   Positive outcomes of Pap smears

As part of quality assurance measures it is important a for a Pap smear provider to seek feedback from patients. Positive outcomes of a Pap smear may include[47, 48]:

- a satisfactory cervical smear is obtained

- minor cell changes are detected early and appropriately managed

- the woman is given appropriate referral for the management of any abnormalities noted

- the woman and Pap smear provider decide the appropriate process for the notification of the Pap smear test results and this plan is adhered to

- the role and benefit of the Cervical Cytology Registry of WA are explained to the woman

- the woman expresses positive satisfaction with her Pap smear examination

- the woman knows when her next Pap smear is due

- the woman continues to participate in regular cervical screening

7.2   What are common errors in Pap smear preparation?

Pap smear providers are responsible for the correct preparation, fixation (preservation) and staining of specimens. Mistakes which may seriously interfere with the correct cytological interpretation of the slides may include[47, 48]:

- use of slides which are not clean

- excess use of lubricants

- insufficient cells collected

- excessive blood associated with collection or menstrual cycle

- excessive inflammatory cells in cases where there is evidence of purulent discharge

- cells collected from the incorrect site i.e. vaginal walls instead of cervix

- incorrect application of cells onto slides
- time delay in applying fixation spray
- insufficient or excess fixation spray used to cover cells on the slide

7.3   The Pap smear assessment

Depending upon the clinical environment in which the Pap smear provider practises, the order of these steps may need to be altered to adapt to the woman's requirements [47, 48].

Obtain a thorough gynaecological or obstetrical history, particularly any:

- postmenopausal bleeding (PMB) or spotting
- postcoital bleeding (PCB) or spotting
- intermenstrual bleeding (IMB) or spotting
- abnormal vaginal discharge

Assessment of the woman prior to the Pap smear determines:

- the need for additional investigations
- the position to be adopted by the woman during the procedure
- the speculum size to be used
- ways in which to ensure the woman's comfort (both physical and psychological) throughout the procedure
- need for referral

7.4   The Pap smear examination

Pap smear providers need to ensure women receive personal care that is sensitive, appropriate, and due regard is given to safety, comfort and dignity throughout the procedure. The steps below are suggested as a guide:

1. Explain the procedure, meaning of the test and results. Make a plan for Pap smear result notification

2. Position the woman comfortably. The supine position is usually best, with the knees slightly bent and falling apart. Cover the woman's lower half with a sheet to create a sense of privacy

3. As the procedure is carried out, explain each step to the woman (if she desires)

4. Inspect external genitalia for any abnormalities

5. Moisten and warm the speculum with water. If lubricant is used, use it sparingly and avoid contact with the cervix

6. Gently part labia and slowly insert closed speculum at a posterior angle into the vagina. Observe the patient for signs of discomfort and encourage feedback throughout the procedure

7. Open speculum to allow visualisation of the cervical external os

8. If there is any difficulty in visualising the cervical external os;

   a. If the cervix is obscured by the lateral vaginal walls bulging inwards, consider using a larger speculum or applying a condom over the speculum (cut off the reservoir tip of the condom so you can sample the cervix) to support the lateral vaginal walls and offer better visibility

   b. Ask the woman to lift her buttocks slightly off the bed temporarily, and place either a rolled towel or ask her to place her clenched fists under her buttocks (this assists in the visualisation of a posterior cervix)

   c. Close and then reinsert speculum at an anterior angle (this assists in visualisation of an anterior cervix)

   d. If still unable to locate the cervix, close the speculum and withdraw it from the vagina. Palpate the position of the cervix with a gloved hand, moistened with water, preferably not lubricant. Once the position of the cervix has been located, reinsert the speculum into the vagina at the appropriate angle

9. Inspect the cervix for the following:

   - colour, size, shape
   - position
   - lesions
   - surface characteristics
   - squamocolumnar junction
   - discharge

   Note: if visual inspection of the cervix is abnormal, the woman requires specialist referral as soon as possible (regardless of the Pap smear result)

10. Take the Pap smear sample and other samples if necessary

11. Close the speculum and remove from the vagina

12. Offer the woman a tissue and panty liner if required

7.5   Completing the Pap smear pathology form

Accurate documentation is essential when delivering cervical screening services. The appropriate clinical management of the woman requires that the woman is uniquely identified. The following information will assist the examining laboratory to interpret the Pap smear and make clinical recommendations that are appropriate for each individual woman. These include[48]:

- collector's practice name
- collector's practice address
- patient Medicare number
- cervical or vault smear
- unit/unique medical record number (UMRN)
- name (previous surname if applicable)
- date of birth
- address
- date of Pap smear
- date of last normal menstrual period (LNMP)
- previous abnormal smear results or treatment
- pregnancy (gestation)
- hormonal therapy: hormone replacement therapy, oral contraceptive pill, Implanon, Depo Provera etc
- hysterectomy
- abnormal symptoms such as postcoital bleeding (PCB) or spotting and intermenstrual bleeding (IMB) or spotting
- abnormal or suspicious appearance of the cervix

7.6 Management of women with screen detected cervical abnormalities

Women who are symptomatic need to be clinically managed in accordance with their presenting history and symptoms. Women who may require specific clinical management outside the NHMRC guidelines include those who present with symptoms such as:

- intermenstrual bleeding or spotting
- postcoital bleeding or spotting
- postmenopausal bleeding or spotting

Women with any of the above symptoms or any other signs or symptoms of concern should be immediately referred for further tests to a specialist gynaecologist so that their condition can be clinically assessed and an appropriate management plan formulated[49].

7.7 Referral of women with screen detected cervical abnormalities

The Pap smear provider must have knowledge of health care agencies and community resources available to women for follow-up care and treatment of cervical abnormalities[48]. A diverse range of health care providers and resources available within the immediate locality need to be provided to the woman so that she has a range of options for her follow-up and treatment plan[48].

When a cervical abnormality has been detected, a letter of referral is sent to the patient's nominated GP (or other medical provider) along with a copy of her Pap smear result[48].

A request for confirmation that the referral and Pap smear result has been received by the health care provider should be included in the letter. The patient should also be provided with a copy of the referral letter that was sent to her health care provider. It is the responsibility of the Pap smear provider to ensure that the referral is sent and received in a timely manner[48].

All steps taken to encourage the woman to attend for follow-up should be clearly documented in the woman's record. For medico-legal reasons, the Pap smear provider must keep documented evidence of all correspondence relating to the follow-up of abnormal results[48].

7.8   Interpretation of Pap smear reports

The Pap smear provider should provide the woman with information regarding her cervical screening result. Should a cervical abnormality be detected, the Pap smear provider should assist the woman in understanding the meaning of her Pap smear result. The Pap smear provider should advise the woman clearly about her follow-up or treatment options to aid her in making an informed decision[47, 48]. The Pap smear provider then needs to make an appropriate referral based on the woman's choice, and clearly document the outcomes of the consult.

The Pap smear report

The Pap smear provider will receive the Pap smear result within two to 14 days, depending upon where the specimen was collected and where it was examined. Pap smear report forms may differ in their format; however, they contain similar information. This section will also note whether it is a conventional Pap smear sample or a Thin Prep® sample. The information on a Pap smear report includes:

Specimen: Identifies the site of the cytology sample.
Possible explanations are:
- Slide Pap smear - Cervical
- Slide Pap smear - Vault

Result: Identifies if the result is negative or abnormal or not suitable for analysis.
Possible results include:
- Unsatisfactory
- Negative for intraepithelial lesion or malignancy
- Possible low-grade squamous intraepithelial lesion
- Low-grade squamous intraepithelial lesion
- Possible high-grade squamous intraepithelial lesion
- High-grade squamous intraepithelial lesion
- Atypical glandular cells
- Possible high-grade glandular lesion
- High-grade glandular lesion

Specific diagnosis:

A more detailed description of the result is given in this section of the report. Along with the report on the presence or absence of any cellular abnormality, the coexisting presence of specific microorganisms may be given. This part of the report also includes a comment on the presence or absence of an endocervical component.

National Health and Medical Research Council Recommendations:

Recommendations are according to the National Health and Medical Research Council screening to prevent cervical cancer: *guidelines for the management of asymptomatic women with screen detected abnormalities*[49] .

Unsatisfactory Pap smear

If a woman has an unsatisfactory smear she will be asked to have another Pap smear in approximately 6 to 12 weeks. The laboratory report should state why the Pap smear was unsatisfactory and may include reasons such as[49]:

- the cells may be obscured by blood or inflammation / mucous
- there may not be enough cells on the sample to give an accurate assessment
- the cells may be atrophic and difficult to interpret
- the smear may not have been properly prepared
- the slide may have broken during transit to the laboratory

Atrophic smears can be difficult for the cytologist to interpret. Atrophic Pap smears commonly occur in postmenopausal and postnatal women, particularly if they are breastfeeding. These unsatisfactory Pap smears result from decreased oestrogen levels, which affect the quality of the cervical cells. It is recommended that if the Pap smear is unsatisfactory due to atrophic changes, the woman has a repeat Pap smear in 3 months after being treated with local oestrogen.

An unsatisfactory Pap smear due to inflammation may be caused by an infection such as Candida spp or Trichomonas. Pap smears may detect the cause of the inflammation; however, additional investigations should be undertaken to identify and treat the cause. Once the cause is treated, the woman should return within 3 months for a repeat Pap smear.

Negative Pap smear

A negative Pap smear result for asymptomatic women who have no history suggestive of cervical pathology would have a recommendation of repeat Pap smear in 2 years.

Possible or definite low-grade squamous intraepithelial lesion (LSIL)

This result indicates minor squamous cell changes that are often due to an acute infection with human papillomavirus (HPV). A woman with a Pap smear report of LSIL should be managed in the same manner, irrespective of whether the cervical abnormality is reported as possible or definite LSIL, and offered a repeat Pap smear in 12 months[49].

Women aged 30 years or more with a possible or definite LSIL, without a negative Pap smear history in the preceding 2 to 3 years are managed differently. These cohorts of women need to have an immediate colposcopy or a repeat Pap smear within 6 months[49]. The reason for this management approach is two-fold: 1) health care providers may be concerned that an occult HSIL will remain undetected and progress to cancer, and 2) health care providers may be concerned that women will not comply with cytological surveillance[49].

Possible or definite high-grade squamous intraepithelial lesion (HSIL)

Women with a possible or definite HSIL should be referred to a gynaecologist for colposcopic assessment and targeted biopsy[49]. This result represents suspected or definite changes commonly associated with a persistent HPV infection which, if left untreated, may progress to cervical cancer[49].

Cervical glandular abnormalities

A Pap smear result reporting adenocarcinoma, endocervical adenocarcinoma in situ, possible high-grade glandular lesion, atypical endocervical or endocervical cells of undetermined significance, should be referred as soon as possible to a gynaecologist with expertise in colposcopic evaluation of suspected glandular malignancies, or a gynaecological oncologist[49].

8. Result follow-up and notification

The National Pathology Accreditation Advisory Council (NPAAC) requires pathology laboratories that report cervical cytology process 90% of smears within 5 working days. The turnaround time for notification of Pap smear results can vary from 5 to 14 days depending on the location of the laboratory and Pap smear provider. The quick turnaround times support Pap smear providers in promptly following-up and treating screen detected cervical abnormalities. Laboratories are responsible for ensuring communication of Pap smear results, in writing, directly to the Pap smear provider. It is not the laboratories responsibility to notify a woman directly, or to provide them with a copy of their Pap smear result. The responsibility of communicating with a woman rests with the Pap smear provider. If you are not the primary health care provider for the woman, you should request a copy be forwarded to the woman's nominated provider to promote continuity of care.

During the Pap smear consultation, the Pap smear provider must establish a mutually acceptable method of notifying the woman of her Pap smear result. Pap smear providers have a duty of care to the woman they provide cervical screening services to; therefore, they must have appropriate systems in place to review and follow-up all Pap smear results. The Pap smear provider is required to ensure that a woman is informed of her cervical test result and that the information is provided to her in a way that she understands. During this explanation it is a good time to advise the woman when her next Pap smear is due.

It is the woman's responsibility to follow this advice and ensure that the Pap smear provider has her current demographic details (i.e. her most current address). In the event that the Pap smear provider is unable to contact or follow-up a woman, it is recommended that the Pap smear provider record all attempts made to contact her. For example the Pap smear provider should record the date and time the woman was phoned, if a letter was sent to her. Documentation of such attempts to contact the woman is an important risk management strategy.

The Cervical Cytology Registry (CCR) of WA also plays an integral role in reminding women when they are overdue for the next Pap smear and in following-up women that have had an abnormal Pap smear. It is important to understand that the CCR is not a 'reminder service' for health care providers. The CCR is a 'safety net' for women throughout WA and through direct mail will advise women and their health care provider when cervical screening tests are overdue. The 'safety net' is enacted in accordance with the *WA Protocol of Actions for Reminder and Follow-up Letters* (see Appendix B).

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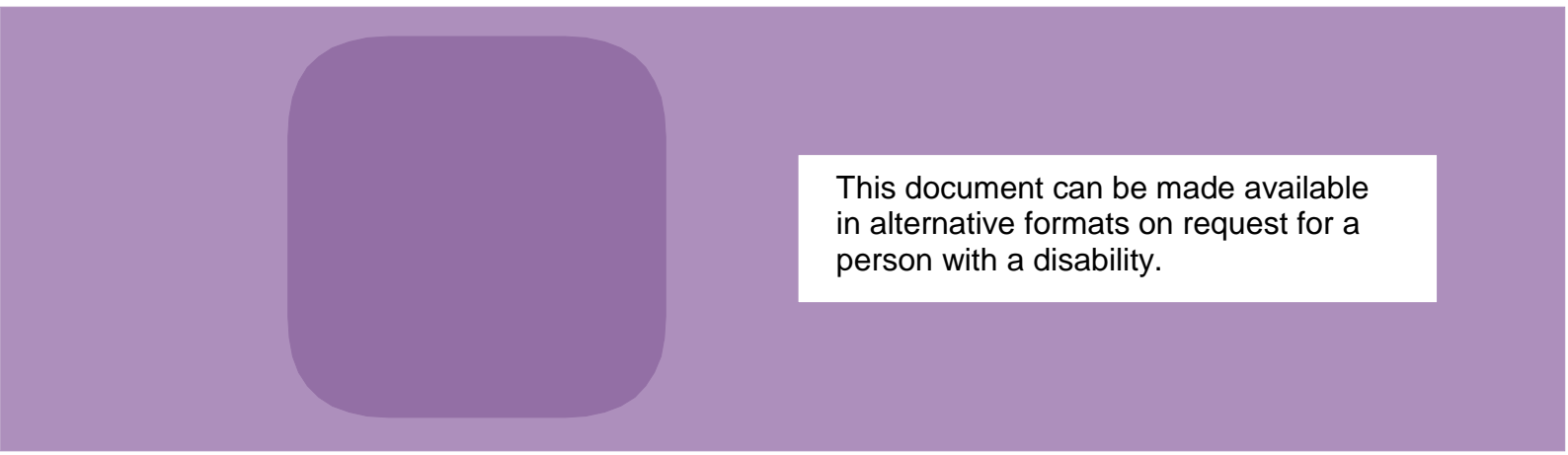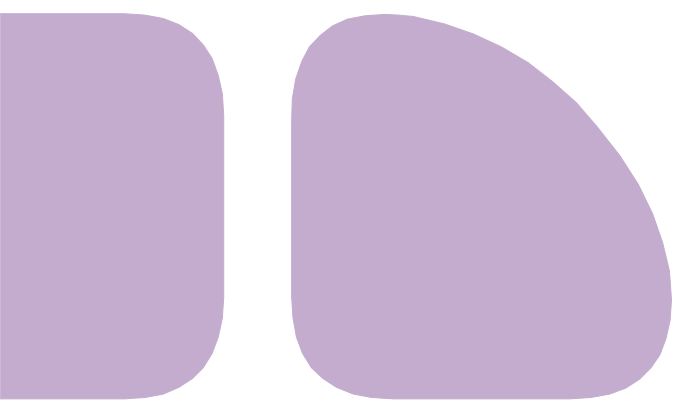DOI:10.1038/sj.onc.1206629.

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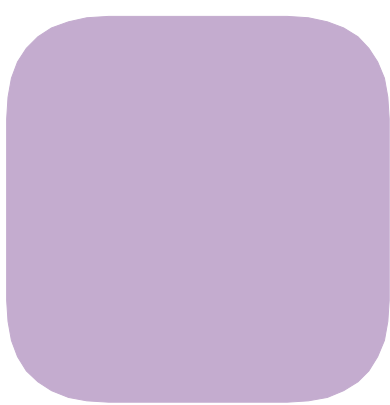
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HIGH-GRADE CERVICAL ABNORMALITY FOLLOWING THE CYTOLOGIC DIAGNOSIS OF ATYPICAL ENDOCERVICAL CELLS OF UNDETERMINED SIGNIFICANCE: A RETROSPECTIVE STUDY OF 1736 CASES

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Background

In 2006, Australia adopted a revised cervical cytology terminology system—the *Australian Modified Bethesda System (AMBS)*. One substantial change in the AMBS was the introduction of the diagnostic category of atypical endocervical cells of undetermined significance (AEC).

Previous studies have reported patients with AEC on cervical cytology to be high-risk for premalignant and malignant cervical disease. To our knowledge this is the first Australian study to investigate the clinicopathological correlations of AEC on cervical cytology.
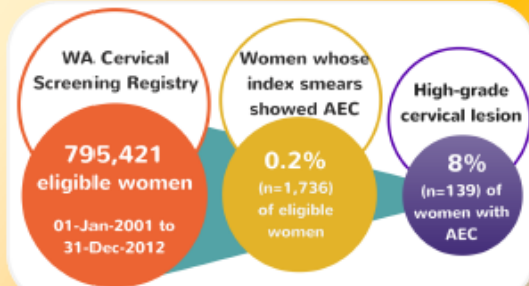
Aim

To determine the incidence, and investigate histological correlations and clinical management of patients presenting with AEC on cervical cytology.

Methods

- A retrospective population based follow-up study.
- Cytology and histology results were extracted from the Western Australia Cervical Screening Registry from 1st Jan 2001—31st Dec 2012.
- All cervical test results prior to 2004 were recoded to reflect the AEC category by an expert working group.
- Time to event analysis was used to predict the odds of having or developing *in situ* and invasive cervical neoplasia.

Results

WA Cervical Screening Registry
795,421 eligible women
01-Jan-2001 to 31-Dec-2012

Women whose index smears showed AEC
0.2%
(n=1,736) of eligible women

High-grade cervical lesion
8%
(n=139) of women with AEC

One hundred thirty nine patients (8.0%) had, or subsequently developed, a high-grade cervical lesion.

Younger women aged 25 to 34 years were fives time more likely to be histologically confirmed with a high-grade cervical lesion compared to patients aged 45-54 years (HR 5.1, 95% CI 3.1—10.2).

Overall, 55.1% of patients underwent evaluation by a specialist with a positive trend in compliance following the revised management guidelines.

The positive predictive value of a high-grade cervical abnormality in patients with AEC increased during the review period.

In addition to high-grade cervical lesions, it should be noted that 33 additional patients with AEC proved to have endometrial carcinoma on follow-up. These cases will be subject to a separate review.

Implications for practice

Cytologic demonstration of AEC requires careful gynaecologic evaluation, particularly in younger patients with no cervical screening history and/or having a previously detected low-grade cervical dysplasia. Australia has proposed that it will adopt a 5-yearly cervical screening interval using primary HPV test; however, reflex liquid-based cytology testing will be performed for women with a high-risk HPV test result. Consequently, reflex cytology tests may still report a finding of AEC and thus the findings from this study are still applicable in the Australian setting.

Government of **Western Australia**
Department of Health
WA Cervical Cancer Prevention Program

Curtin University

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Additional material 5: Presentation delivered at the University of Western Australia's Rising Stars Forum

The clinical importance of atypical endocervical cells of undetermined significance

Aime Munro
WA Cervical Cancer Prevention Program
Centre for Population Health Research, Curtin University
School of Women's and Infants' Health Research, UWA

Background

- In 2006, Australia adopted a revised cervical cytology terminology system, known as the *Australian Modified Bethesda System (AMBS)*.

- One substantial change was the introduction of the diagnostic category of atypical endocervical cells of undetermined significance (AEC).

- An AEC test result is an uncommon cervical cytology finding, less than 1% of Pap smear tests.

- Most previous studies on AEC were limited by short follow-up intervals and small numbers of cases.

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Methodology

- A retrospective cohort study from 2006-2012
- Women followed up from time of first AEC cytology test result until their last cytology record or until a biopsy confirmed high grade lesion
- Survival analyses used to identify factors associated with risk of high-grade lesions

Results

- There were 559 women in the cohort with an AEC cervical cytology
- 65 women went on to develop high-grade cervical lesions
- Survival analyses show significant predictors of high grade lesions were age at AEC and screening history

Results (cont'd) – histology outcomes

Histology outcomes	Age group (years)					
	≤ 24	25-34	35-44	45-54	≥ 55	Total
Unsatisfactory	0	0	0	0	2	2
Normal	8	30	75	72	27	212
Low grade*	9	7	17	10	6	49
High-grade intraepithelial lesions						
CIN 2	0	3	5	1	0	9
CIN 3	3	9	5	1	0	18
ACIS	6	20	10	1	1	38
Cervical malignancy						
Adenocarcinoma	0	2	0	1	0	3
Adenosquamous carcinoma	0	1	0	0	0	1
Endometrial carcinoma	0	0	1	5	17	23
Total	26	72	113	91	53	355

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Results – survival regression analysis

	Hazard rate ratio	95% CI	P-value
Age (years)			
≤ 24	1.2	0.5 – 2.7	0.647
25 - 34	2.3	1.3 – 4.0	0.003
35 – 44 (reference group)	1.0		
45 – 54	0.1	0.1 – 0.5	0.001
≥ 55	0.1	0.1 – 0.9	0.034
Importance of screening interval prior to index AEC (years)			
Never screened	2.5	1.4 – 4.6	0.003
≤ 1 and required follow-up	2.7	1.2 – 6.2	0.015
≤ 1 year early reecreen	0.8	0.2 – 3.4	0.742
≥1 year although required follow-up	3.1	1.1 – 8.9	0.033
≥ 1 to 4 years no follow-up was required (reference group)	1.0		
≥ 4 years	1.7	0.7 - 3.8	0.208

Delivering a **Healthy WA**

Results

- Older women presenting with AEC tended to develop endometrial cancer rather than high-grade cervical lesions.

Conclusion

- Cytologic demonstration of AEC requires careful gynaecologic evaluation, particularly in younger women who are at greater risk of high-grade squamous (CIN) or glandular (ACIS) lesions, while in older women the possibility of endometrial neoplasia needs to be considered.

Acknowledgements

- **WA Cervical Cancer Prevention Program employees**
  - Ms Nerida Steel
  - Ms Christine Fletcher

- **School of Women and Infants' Health, University of Western Australia**
  - Professor Yee Leung
  - Dr Paul Cohen
  - Dr Colin Stewart

- **Centre for Population Health Research, Curtin University**
  - Professor James Semmens
  - Professor Peter O'Leary
  - Associate Professor Vincent Williams
  - Dr Jim Codde
  - Dr Katrina Spilsbury

Delivering a **Healthy WA**

CKC or LEEP for ACIS
What is the Gold Standard?

on behalf of
A Munro, Y Leung, K Spilsbury, CJR Stewart, J Semmens,
J Codde, V Williams, P O'Leary, N Steel, P Cohen

ASGO Penang 2015

Conflicts

Member, WA Cervical Cancer Prevention
Program Advisory Group

ACIS

What is the "gold standard"?

What is a cone biopsy?

Why is the gold standard not followed?

What are the clinical outcomes for LEEP versus
CKC?

"Gold standard"

Guideline — Cone biopsy for the assessment of glandular lesions	
Cold-knife cone biopsy should be considered the 'gold standard' for the assessment of glandular lesions.	Consensus

NHMRC Guidelines 2005 (p67)

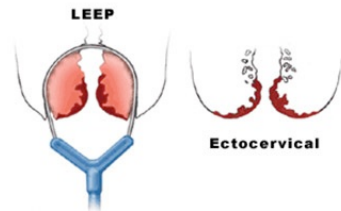THE UNIVERSITY OF WESTERN AUSTRALIA

"Gold standard"

"Cone biopsy should be tailored according to the colposcopic findings and the patient's age and childbearing requirements."

NHMRC Guidelines 2005 (p67)

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"Gold standard"

ACIS
85% <15mm from SCJ
<36yo usually <10 mm

Older women are more likely to have more extensive lesions … requiring deeper excisions

Nicklin JL, et al. ANZJOG 1991; 31(2):179–183

"Gold standard"

Size

Margins

Specimen number

Complications
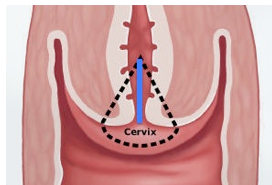
Cone biopsy

Cone biopsy is indicated for the further assessment and treatment of a woman with a cytology report predicting AIS. There are several methods of cone biopsy. These include cold-knife cone, laser cone, large loop excision of the cervical TZ (LLETZ) and Fisher cone. Cold-knife cone biopsy should be considered the 'gold standard'.

Data suggest that women treated by LLETZ tend to undergo shallower procedures with higher rates of endocervical margin involvement, and LLETZ is therefore best avoided for this purpose (Widrich et al 1996, Wolf et al 1996, Azodi et al 1999). There are very little data regarding the use of either laser or Fisher cone for the management of glandular abnormalities.

Cone biopsy should be tailored according to the colposcopic findings and the patient's age and childbearing requirements.

NHMRC Guidelines 2005 (p67)
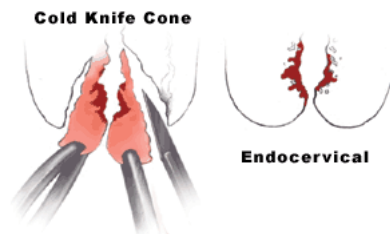
Australian case-series data confirm that 85% of AIS will extend to less than 15 mm from the SCJ (Nicklin et al 1991). However, the SCJ may not always be visible and the proximal linear extent of AIS may be as far as 25 mm along the canal from the SCJ. The proximal linear extent of AIS is related to age. Women under 36 are unlikely to have disease extending more than 10 mm from the SCJ, allowing for more limited excision.

Older women are likely to have more extensive lesions and require deeper excisions of at least 25–30 mm (Nicklin et al 1991).

NHMRC 2005 (p90)

ACIS

What is actually happening?

What are the clinical outcomes for LEEP versus CKC in ACIS?

CKC vs LEEP

Patient age <30/≥30

Socio Economic Index for Area

Histopathology – modality, depth, margin status, number of specimens

CKC vs LEEP

Retrospective, population based

Registry data from 2001 – 2012

18 years and older

Western Australia

ACIS diagnosed on Pap/biopsy

CKC vs LEEP

Follow-up

Clinical outcomes

CKC vs LEEP

338 cases

231 CKC
(68.3%)

107 LEEP
(31.7%)

CKC vs LEEP

231

107

Significant difference

Number of specimens
Specimen depth
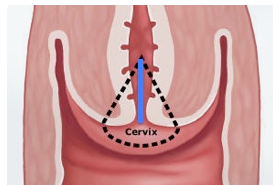
CKC vs LEEP

231   107

Margin status

Not significant (p = 0.432)

69.7%	Negative margin	62.6%
25.5%	Positive margin	31.8%
4.8%	Indeterminate margin	5.6%

CKC vs LEEP

Margin status

When adjusted for margin status, no statistically significant difference between

    age, SEIFA, coexistent CIN

    specimen depth

    modality

and ACIS persistence/recurrence

CKC vs LEEP

Margin status

3.4 times increased rate (95% CI 1.5 – 7.8) of
ACIS persistence /recurrence if positive margin

CKC vs LEEP

Outcomes <12 months

24 (7.1%) had persistent ACIS

    10 had negative margin

        4.4% overall risk of persistent ACIS even if negative margin

8 (2.4%) risk endocervical adenocarcinoma

CKC vs LEEP

CONCLUSIONS

Ideal to have single specimen

Ideal to have adequate depth...but even with negative margins, overall 4.4% risk of persistent ACIS

CKC vs LEEP

CONCLUSIONS

No significant difference in margin status between CKC and LEEP

No difference in ACIS persistence or recurrence between CKC and LEEP

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