Australian Government
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Report on monitoring activities of the National Cervical Screening Program Safety Monitoring Committee

CANCER SERIES NO. 80

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Authoritative information and statistics to promote better health and wellbeing

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Contents

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Abbreviations

AIHW	Australian Institute of Health and Welfare
AS	age-standardised
CI	confidence interval
DoHA	Department of Health and Ageing
HPV	human papillomavirus
NCSP	National Cervical Screening Program
NHMRC	National Health and Medical Research Council
NPAAC	National Pathology Accreditation Advisory Council
Pap test	Papanicolaou test to detect cervical cell abnormalities
RCPA	Royal College of Pathologists of Australia
SMC	Safety Monitoring Committee
VCS Pathology	Victorian Cytology Services Pathology laboratory

Summary

It has been 7 years since the National Health and Medical Research Council altered its guidelines on how women with a low-grade Pap test result or a treated high-grade cervical biopsy result should be managed.

This report looks at the evidence that the Safety Monitoring Committee collected to evaluate effects of this change. This Committee was established to assess whether there were adverse outcomes following the introduction of the new guidelines.

Based on its assessment of the evidence, the Committee determined that:

- the change in management for women with a low-grade Pap test result has not led to an increase in cervical cancer
- women who complete 'test of cure' after being treated for a high-grade cervical biopsy result have a very low rate of subsequent high-grade biopsy results, and to date none have developed cervical cancer
- limited data were available to audit cancer cases but it appeared that a range of factors may have contributed to the cancers that did arise after the detection of cytological abnormalities
- attendance by women for a follow-up test within 3 months of the recommended interval is generally high, although based on the evidence, women aged less than 30 are less likely to attend within 15 months of their initial low-grade Pap test result than women aged over 30
- attendance has been lower than recommended among women with a recent low-grade Pap test result whose first follow-up test was negative, possibly due to women considering themselves 'safer' after this negative test
- overall laboratory recommendation codes were broadly concordant with the changed management guidelines, although concordance was lower for low-grade management exceptions, that is women over 30 and those who had a second low-grade abnormality. There is evidence that the use of automated decision support tools in laboratories assists them to comply with the new guidelines.

The projects undertaken under the auspices of the Safety Monitoring Committee contribute to a current picture of the safety of the *NHMRC Guidelines for the management of screen detected abnormalities in asymptomatic women* introduced in Australia in July 2006, compared to the previous NHMRC Guidelines that were rescinded at that time.

Acknowledging that new evidence may come to light in future which could affect this picture, the overarching message from the evidence currently available and the methods used to assess this evidence is that the new guidelines have not led to an increase in cervical cancer in the 7 years since they were introduced.

1 Introduction

1.1 Why have guidelines?

There are over 2 million Papanicolaou smears, or 'Pap tests' to detect cervical cell abnormalities performed on Australian women each year, with around 110,000 of these detecting abnormal cells (AIHW 2013). The detection and management of abnormalities—particularly 'high-grade' abnormalities—is the way in which the National Cervical Screening Program (NCSP) prevents the development of cervical cancers, thereby achieving its aim of reducing cervical cancer cases, as well as illness and death resulting from cervical cancers.

Guidelines enable practitioners and clinicians to manage the 110,000 abnormalities detected each year according to evidence-based information which guides best practice.

The National Health and Medical Research Council's (NHMRC) *Screening to prevent cervical cancer: Guidelines for the management of asymptomatic women with screen detected abnormalities* ('the NHMRC Guidelines') (NHMRC 2005) provides recommendations for the management of women with an abnormal Pap test result. They enable practitioners and clinicians to manage these 110,000 abnormalities detected each year according to evidence-based information which guides best practice.

The latest guidelines were approved in June 2005 and implemented from 3 July 2006, and replaced the previous 1994 guidelines, which were rescinded. Formulated in line with the NHMRC standards for clinical practice guidelines available at that time, these guidelines are based on epidemiological and scientific evidence and a new understanding of the role of human papillomavirus (HPV) in cervical cancer (DoHA 2012).

1.2 Why monitor the safety of these guidelines?

The 2005 NHMRC Guidelines included management recommendations that were significantly different to the previous 1994 guidelines. They included:

- changed recommendations for the management of women with a low-grade squamous abnormality (possible or definite low-grade squamous intraepithelial lesion) on cytology, with most women with this result recommended to have a repeat Pap test in 12 months
- a new management approach for women who have been treated for high-grade intraepithelial disease, recommending that they now undergo a 'test of cure' process, whereby cervical cytology and human papillomavirus (HPV) tests are conducted at 12-month intervals and if both are negative on two consecutive occasions, the woman is returned to the usual 2-yearly screening interval.

As these were significant changes to the way women are managed, in late 2005 a Safety Monitoring Committee (SMC) was established to monitor the safety of these recommendations and provide timely review of policy as needed.

Safety Monitoring Committee (SMC)

The SMC comprises relevant experts, including representatives from the Royal Australian College of General Practitioners, the Royal College of Pathologists of Australasia (RCPA), the Royal Australian and New Zealand College of Obstetricians and Gynaecologists, the

Australian Society for Colposcopy and Cervical Pathology (ASCCP), the Australasian Association of Cancer Registries (AACR) and the Australian Institute of Health and Welfare (AIHW), as well as a National Cervical Screening Program (NCSP) program manager and data manager, a consumer representative, statisticians and epidemiologists, and officers of the Department of Health (DoH).

The SMC reports to the Standing Committee on Screening (formerly the Screening Subcommittee) of the Community Care and Population Health Principal Committee (formerly the Australian Population Health Development Principal Committee). Both Committees were renamed in early 2012.

Box 1.1: Clinical terminology

Because the management guidelines are intended for a clinical audience, use of clinical terms is unavoidable; the following provides a brief guide to the main clinical terms used.

Uterine cervix, or simply **'the cervix'** is the neck of the uterus or 'womb'. The cervix is comprised of **squamous** cells on the outer part of the cervix and **glandular** cells in the endocervical canal (the 'transformation zone' where squamous and glandular cells meet is where abnormalities and cancer are usually found).

Cytology is the examination of cells from the cervix through a microscope. These cells are usually collected by a Pap test, which is the screening test of the National Cervical Screening Program.

The terms intraepithelial **lesion**, intraepithelial **disease** and **abnormality** are used interchangeably, and all refer to the presence of abnormal cells in the epithelial layers of the lining of the uterine cervix.

Abnormalities are graded depending on how much of the lining of the cervix abnormal cells occupy; '**low-grade**' abnormalities are contained in the top layer of the lining of the cervix, while '**high-grade**' abnormalities occupy more layers.

1.3 How has the safety of the guidelines been monitored?

The SMC has undertaken several projects to fulfil its role of assessing the safety of the guideline recommendations for the management of women with a low-grade cervical cytology result and women treated for high-grade intraepithelial disease.

The primary project, and a modification of the process recommended by the Guidelines Review Group outlined in appendices 12 and 13 of the guidelines (NHMRC 2005), has been a major statistical analysis that the AIHW performed using cervical cytology register data. This was to determine if there has been an increase in the risk of cervical cancer in women following a low-grade cervical cytology or treated high-grade histology under the 2005 guidelines compared to the 1994 guidelines. Results of these analyses were provided to the SMC in 6-monthly reports, with each report extending the period of data collection under the 2005 guidelines by 6 months.

Supplementing this primary project are a cancer case review of all cervical cancer cases diagnosed in women after a low-grade cervical cytology result and in women treated for high-grade intraepithelial disease; a laboratory survey; an assessment of laboratory compliance with guideline recommendations; and an assessment of national cervical cancer incidence data.

The SMC assessed these projects in-house for some time in advance of sufficient data being available to reach firm conclusions that could be made publicly available. The SMC agreed that a 'warning' flag would be raised if safety monitoring parameters exceeded expected levels at the 10% α-level and an 'immediate action required' flag if the parameters exceeded expected levels at the 5% α-level. Through this mechanism, important results would be made available promptly and immediate action taken if it became apparent that the new guidelines were unsafe.

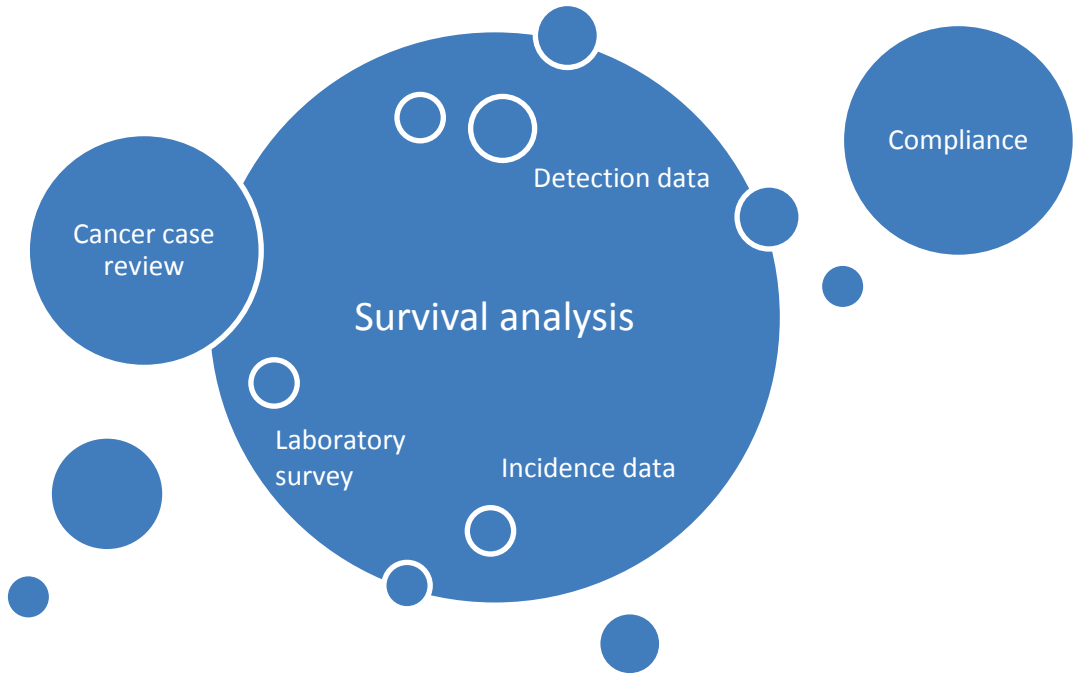


Figure 1.1: The projects used by the Safety Monitoring Committee to assess the safety of the new NHMRC Guidelines

2 Consideration of background trends in cervical abnormalities and cancer

Any trends that may emerge from the projects undertaken under the auspices of the SMC do so within a broader cervical screening environment. As such, it is important to consider background trends in the prevalence of low-grade and high-grade abnormalities.

Trends in cervical cancer incidence are also important to consider as part of the safety monitoring of the guidelines, since any increase in the incidence of cervical cancer might be a direct result of the change in guidelines implemented in 2006.

This chapter presents the latest data and trends in cervical abnormality detection—sourced from state and territory cervical cytology registers, and cervical cancer incidence—sourced from the Australian Cancer Database (ACD) and provided by state and territory cancer registries.

Box 2.1: Detection versus incidence

When considering the **detection** of abnormalities, it is important to note that, while cervical abnormalities are present in a proportion of women in the population at any one time, these abnormalities can only be detected if these women have a Pap test. Thus, while data on the detection of abnormalities can reflect underlying **incidence** of abnormalities in the population, these data are really conveying how many abnormalities are found through cervical screening, and not how many abnormalities are present.

Incidence, on the other hand, is the true number of cases of disease present in the population, and is the terminology used for cervical cancer trends.

2.1 Cervical abnormalities detected by cytology

In 2011, there were 115,026 abnormalities (low-grade, high-grade or cancer) detected in the 2,025,860 cytology tests for women aged 20–69 (5.6 abnormalities per 100 cytology tests). Of these abnormalities, 84,540 (73.5%) were low-grade and 30,253 (26.3%) were high-grade, with cancer making up the remaining 0.2% (Table 2.1).

Cytologically detected abnormality trends

The detection of low-grade abnormalities decreased steadily from a peak of 114,257 in 2005 to 78,510 in 2010 for women aged 20–69 (this was a decrease from 5.5 to 3.9 per 100 cytology tests, age-standardised). A slight increase from 78,510 in 2010 to 84,540 in 2011 (from 3.9 to 4.1 per 100 cytology tests, age-standardised) was noted but this was still well below the detection rate prior to 2006 (Table 2.1). The trend for a decline in low-grade abnormalities since 2006 is consistent with the change in guidelines for women with a low-grade cytology result, since fewer low-grade cytology tests were repeated under the new guidelines, leading to the observed decrease in the detection of low-grades by cytology results. The longer interval for repeat smears was directed at allowing time for clearance of HPV infection before the follow-up test was undertaken.

The age-standardised detection of high-grade abnormalities remained steady at 1.3 per 100 cytology tests for all years from 2004 to 2007, and was slightly higher from 2008 to 2011

(Table 2.1). There are several possible reasons for this small increase, but it was not a key parameter determined for SMC monitoring, which focused on cervical cancer as the key outcome. Overall, the rate of all abnormalities combined decreased between 2004 and 2011.

Table 2.1: Abnormalities detected by cytology in women aged 20–69, 2004 to 2011

	2004	2005	2006	2007	2008	2009	2010	2011
Low-grade abnormalities								
Number	109,814	114,257	103,841	97,916	92,013	83,933	78,510	84,540
Crude rate	5.4	5.6	5.1	4.7	4.5	4.0	3.9	4.1
AS rate	5.4	5.5	5.1	4.6	4.5	4.0	3.9	4.1
95% CI	5.3–5.4	5.4–5.5	5.0–5.1	4.6–4.6	4.4–4.5	4.0–4.0	3.9–3.9	4.1–4.2
High-grade abnormalities								
Number	26,975	26,534	26,165	28,297	29,176	28,054	28,491	30,253
Crude rate	1.3	1.3	1.3	1.4	1.4	1.3	1.4	1.5
AS rate	1.3	1.3	1.3	1.3	1.4	1.3	1.4	1.5
95% CI	1.3–1.3	1.2–1.3	1.2–1.3	1.3–1.3	1.4–1.4	1.3–1.3	1.4–1.4	1.4–1.5
All abnormalities (low-grade, high-grade and cancer)								
Number	137,010	141,016	130,234	126,442	121,400	112,188	107,261	115,026
Crude rate	6.8	6.9	6.4	6.0	5.9	5.4	5.3	5.6
AS rate	6.7	6.7	6.3	5.9	5.9	5.4	5.3	5.6
95% CI	6.6–6.7	6.7–6.8	6.3–6.4	5.9–6.0	5.8–5.9	5.3–5.4	5.3–5.4	5.6–5.6

Notes

1. Low-grade abnormalities are cytology test results S2, S3 and E2; high-grade abnormalities are cytology results S4, S5, S6, E3, E4 and E5. All abnormalities are cytology results S2, S3, S4, S5, S6, S7, E2, E3, E4, E5 and E6 (see Table 3.1).
2. Crude rate is the number of low-grade, high-grade, or all abnormalities detected by cytology as a proportion of the total number of cytology tests; age-standardised (AS) rate is the number of low-grade, high-grade, or all abnormalities detected by cytology as a proportion of the total number of cytology tests age-standardised to the Australian population at 30 June 2001.
3. Data in this table are based on the number of abnormalities detected, not the number of abnormal cytology tests—in a small proportion of cytology tests there may be more than one abnormality detected, both of which will be counted.

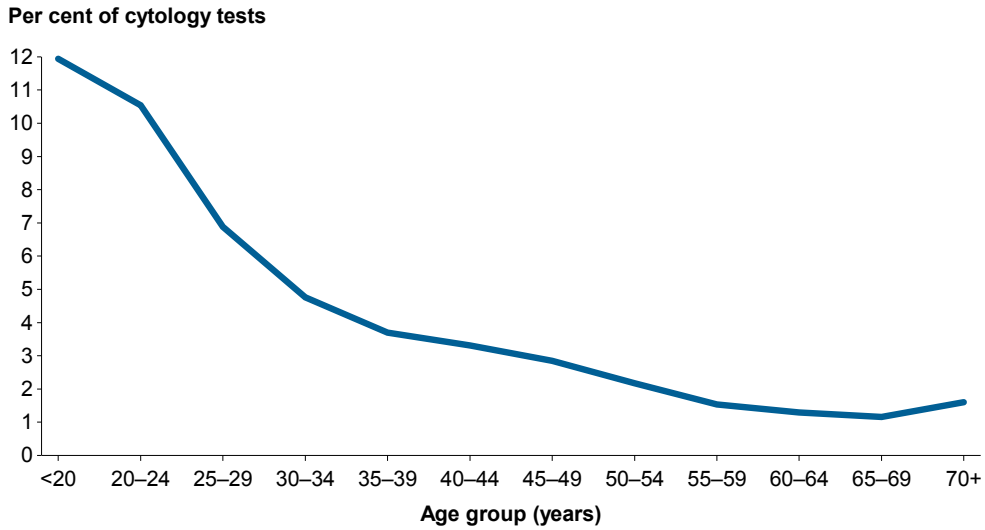
Source: AIHW 2013.

Cytologically detected abnormalities by age

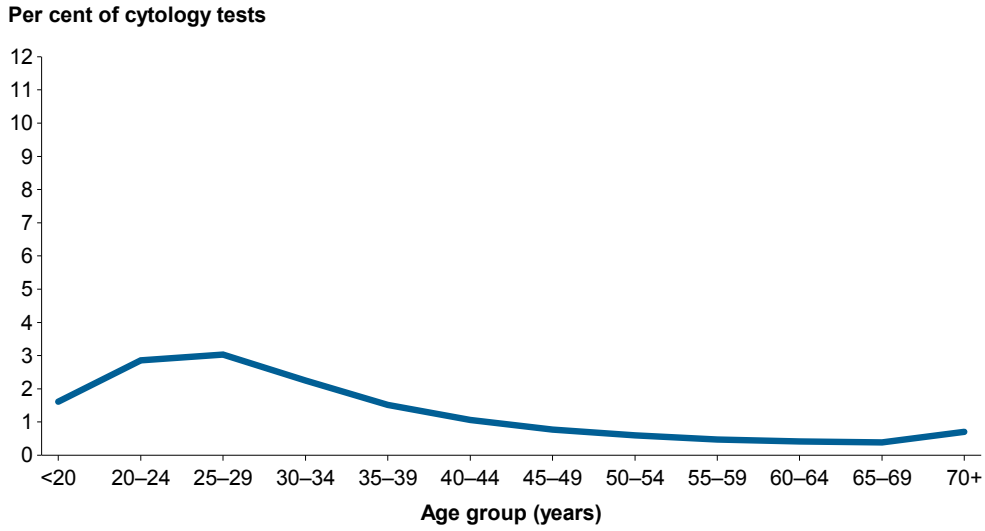
For abnormalities detected by cytology, Figure 2.1A shows the age distribution of low-grade abnormalities and Figure 2.1B the age distribution of high-grade abnormalities.

Abnormalities are most common in younger women, which is attributed to HPV infections that occur frequently after sexual debut. Low-grade abnormalities are highest in women aged less than 20 and in those aged 20–24 (Figure 2.1A), while high-grade abnormalities are relatively low in women aged less than 20 and peak in women aged 20–29 (Figure 2.1B). Detection of both low-grade and high-grade abnormalities then decreases with increasing age, only increasing again in women aged 70 or over (Figures 2.1A and 2.1B).

A



B



Note: The number of low-grade or high-grade abnormalities detected by cytology are shown as a proportion of the total number of cytology tests for each 5-year age-group (crude rates only).

Source: AIHW 2013.

Figure 2.1: Low-grade (A) and high-grade (B) abnormalities detected by cytology, by age, 2011

2.2 Cervical abnormalities detected by histology

In 2011, there were 38,122 abnormalities (low-grade, high-grade or cancer) detected in the 75,589 histology tests for women aged 20–69 (50.4 per 100 histology tests). Of these abnormalities, 14,566 (38.3%) were low-grade and 22,676 (59.6%) were high-grade, with cancer making up the remaining 2.1% (Table 2.2).

Histologically detected abnormality trends

Low-grade abnormalities detected by histology decreased from 20,239 in 2004 to 14,566 in 2011 (Table 2.2). The overall decrease, across all age groups, is in line with expected

changes in detection of low-grade abnormalities resulting from changes to the recommended management of women with low-grade abnormalities as part of the current NHMRC guidelines introduced in 2006. The 2011 data suggest the trend may have stabilised following this change but further data are required in order to confirm this.

Box 2.3: Histology explained

Whereas cytology is performed for all women who participate in cervical screening (since each Pap test performed yields a cytology sample for analysis), histology is only performed on a small proportion of these women. This is because the majority of Pap tests do not detect an abnormality, and thus do not require diagnostic follow-up (unless there is a clinical indication to do so). Usually only high-grade or endocervical abnormalities will be followed by histology, but details of appropriate management are outlined in the current NHMRC guidelines for asymptomatic women.

In contrast, the detection of high-grade abnormalities by histology increased from 19,681 in 2004 to 22,676 in 2011 for women aged 20–69 (an increase from 21.2 to 25.9 per 100 histology tests, age-standardised) (Table 2.2). Again, there are several possible reasons for this increase, but it was not a key parameter determined for SMC monitoring which focused on cervical cancer as the key outcome. Overall, the rate of all histologically detected abnormalities combined remained comparatively steady between 2004 and 2011.

Table 2.2: Abnormalities detected by histology in women aged 20–69, 2004 to 2011

	2004	2005	2006	2007	2008	2009	2010	2011
Low-grade abnormalities								
Number	20,239	19,576	18,003	16,602	15,347	14,576	14,018	14,566
Crude rate	26.5	26.0	24.8	23.2	21.1	20.1	19.4	19.3
AS rate	23.0	22.2	21.4	20.2	18.4	17.6	17.2	17.4
95% CI	22.7–23.4	21.9–22.6	21.1–21.8	19.9–20.6	18.1–18.7	17.3–17.9	16.9–17.5	17.1–17.7
High-grade abnormalities								
Number	19,681	20,200	20,063	21,067	22,102	22,031	22,104	22,676
Crude rate	25.8	26.8	27.7	29.4	30.4	30.4	30.6	30.0
AS rate	21.2	22.0	22.9	24.4	25.2	25.4	25.9	25.9
95% CI	20.9–21.5	21.6–22.3	22.6–23.3	24.1–24.8	24.8–25.5	25.0–25.7	25.6–26.3	25.5–26.2
All abnormalities (low-grade, high-grade and cancer)								
Number	40,653	40,603	38,825	38,476	38,325	37,380	36,940	38,122
Crude rate	53.3	53.9	53.5	53.7	52.7	51.6	51.1	50.4
AS rate	45.5	45.8	45.8	46.2	45.1	44.4	44.4	44.6
95% CI	45.0–46.0	45.3–46.2	45.3–46.3	45.7–46.7	44.7–45.6	43.9–44.9	44.0–44.9	44.1–45.0

Notes

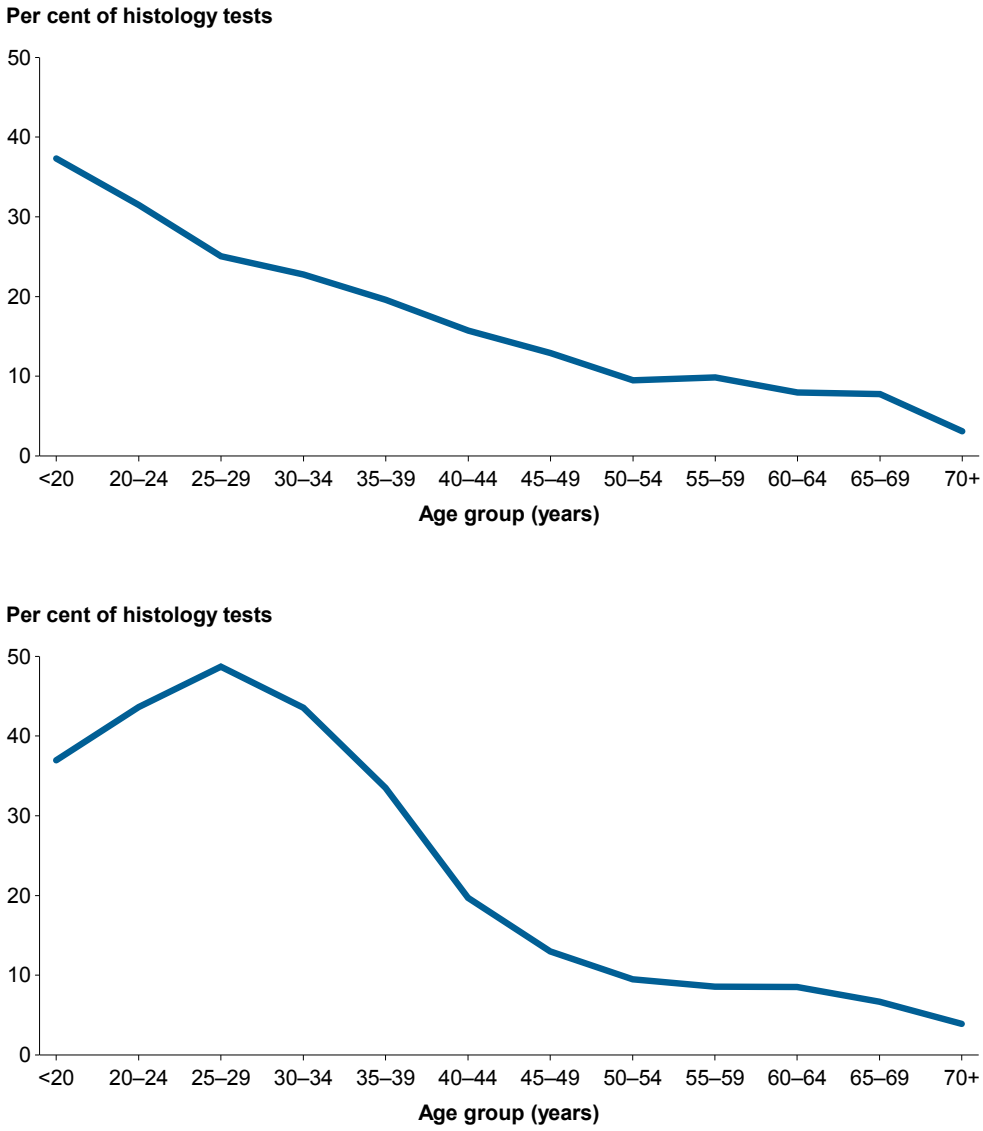
1. Low-grade abnormalities are histology test results HS02 and HE02; high-grade abnormalities are histology results HS03 and HE03. All abnormalities are histology test results HS02, HS03, HS04, HE02, HE03 and HE04 (see Table 4.1).
2. Crude rate is the number of low-grade, high-grade, or all abnormalities detected by histology as a proportion of the total number of histology tests; age-standardised (AS) rate is the number of low-grade, high-grade, or all abnormalities detected by histology as a proportion of the total number of histology tests age-standardised to the Australian population at 30 June 2001.
3. This is the number of abnormalities detected, not the number of abnormal histology tests—in a small proportion of histology tests there may be more than one abnormality detected, both of which will be counted.

Source: AIHW 2013.

Histologically detected abnormalities by age

For abnormalities detected by histology, Figure 2.2A shows the age distribution of low-grade abnormalities and Figure 2.2B the age distribution of high-grade abnormalities.

Similar to abnormalities detected by cytology, abnormalities detected by histology were most common in younger women (HPV infections are common in the years following sexual debut). However, because low-grade cytology is not routinely followed up with histology under the current NHMRC guidelines (NHMRC 2005), low-grade histology was less frequently detected than high-grade histology, and is more reflective of biopsy rates than the true incidence of disease (Figure 2.2A). The age distribution of high-grade abnormalities showed a peak in women aged 20–34, thereafter declining sharply with increasing age (Figure 2.2B).



Note: The number of low-grade or high-grade abnormalities detected by histology are shown as a proportion of the total number of histology tests for each 5-year age-group (crude rates only).

Source: AIHW 2013.

Figure 2.2: Low-grade (A) and high-grade (B) abnormalities detected by histology, by age, 2011

2.3 Women with high-grade abnormalities detected by histology (high-grade abnormality detection rate)

High-grade abnormality detection rate in 2011

The high-grade abnormality detection rate is defined as the number of women (not tests) with a high-grade abnormality detected by histology per 1,000 women screened. This differs from the previous section in which abnormalities were counted, and means that any given abnormality will only be counted once in a calendar year. Presenting the number of women with a high-grade abnormality as a proportion of the number of women screened also yields information that essentially removes the effect of changes in the number of women screened.

High-grade abnormalities have a greater probability of progressing to invasive cancer than low-grade abnormalities (although it should be noted that high-grade abnormalities do not always progress, with one study suggesting that at least 80% of high-grade abnormalities regress spontaneously (Raffle et al. 2003). Detection of high-grade abnormalities provides an opportunity for treatment before cancer can develop, thus the NCSP aims to detect high-grade abnormalities in line with its broader aim to reduce the incidence of cervical cancer.

In 2011, there were 16,635 *women* with a high-grade abnormality detected by histology (different to the number of high-grade *abnormalities* per *100 histology tests* presented in Table 2.2), which equates to a high-grade abnormality detection rate of 8.4 for women aged 20–69 (Table 2.3). This means that, for every 1,000 women screened, 8.4 had a high-grade abnormality found, providing an opportunity for treatment before possible progression to cervical cancer.

High-grade abnormality detection rate trends

The high-grade detection rate increased from approximately 7.7 between 2004 and 2007 to 8.4 per 1,000 women screened in 2011 (Table 2.3). Again, there are several possible reasons. Earlier AIHW data provide evidence of an increase occurring from around 2002 (AIHW 2013).

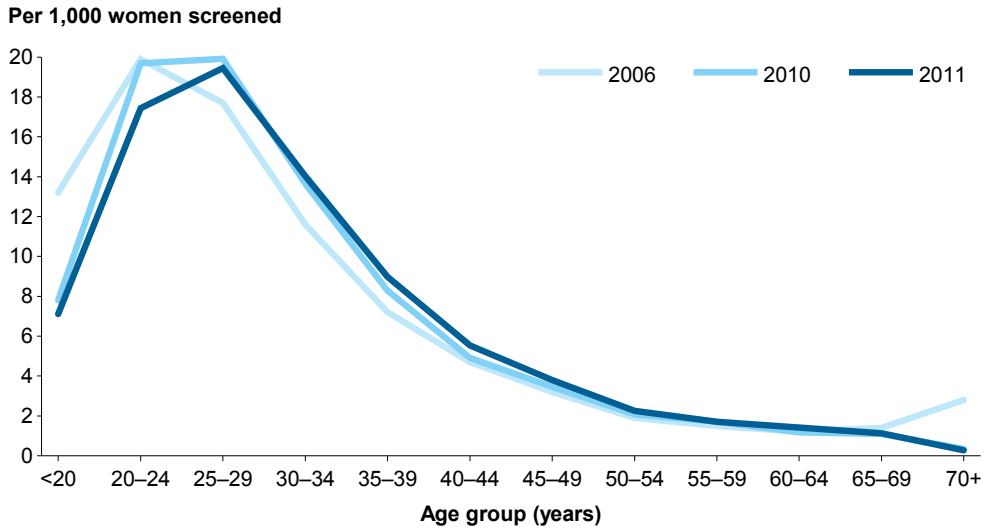
In contrast, there has been a steady decline in high-grade abnormality detection in women aged less than 20. Although this decline appeared to commence earlier, the decrease between 2010 and 2011 from 7.8 to 7.1 for women aged less than 20, and the accompanying decrease from 19.7 to 17.4 for women aged 20–24 between 2010 and 2011 corresponds with the commencement of the HPV vaccination program. [Note: this commenced in 2007, with girls vaccinated during the catch-up program (2007–2009) now becoming eligible for screening (a trend noted in Brotherton et al., 2011).] As the cohort of vaccinated girls becomes older, a decline in the high-grade abnormality detection rate in the 20–24 age group is already apparent in 2011 (Table 2.3; Figure 2.3).

Table 2.3: High-grade abnormality detection rate, by age, 2004 to 2011

Age group (years)	2004	2005	2006	2007	2008	2009	2010	2011
<20	14.5	13.2	13.2	11.6	10.8	8.9	7.8	7.1
20–24	20.3	20.2	19.9	18.9	21.3	19.9	19.7	17.4
25–29	17.7	17.7	17.7	17.8	19.3	19.0	19.9	19.4
30–34	11.6	11.6	11.6	11.5	12.7	12.8	13.6	14.0
35–39	7.1	7.0	7.2	7.3	7.8	7.6	8.3	9.0
40–44	4.6	4.4	4.7	4.7	4.8	4.7	4.9	5.5
45–49	3.1	3.1	3.2	3.2	3.3	3.3	3.5	3.8
50–54	1.7	1.7	1.9	1.9	2.0	1.9	2.1	2.2
55–59	1.5	1.6	1.5	1.4	1.3	1.3	1.7	1.7
60–64	1.2	1.4	1.2	1.2	1.3	1.2	1.2	1.4
65–69	1.0	1.0	1.4	1.3	1.3	1.1	1.1	1.1
70+	3.1	3.0	2.8	2.4	2.6	2.6	3.4	2.7
Ages 20–69								
Crude rate	7.9	7.9	7.8	7.8	8.4	8.1	8.4	8.4
AS rate	7.7	7.7	7.8	7.7	8.3	8.1	8.5	8.4
95% CI	7.6–7.9	7.6–7.8	7.6–7.9	7.5–7.8	8.2–8.5	8.0–8.2	8.3–8.6	8.3–8.6

Note: Crude rate is the number of women with a high-grade abnormality detected by histology per 1,000 women screened; age-standardised (AS) rate is the number of women with a high-grade abnormality detected by histology per 1,000 women screened, age-standardised to the Australian population at 30 June 2001.

Source: AIHW 2013.



Note: The number of women with a high-grade abnormality detected by histology are shown per 1,000 women screened for each 5-year age group (crude rates only).

Source: AIHW 2013.

Figure 2.3: High-grade abnormality detection rate, by age, 2006, 2010 and 2011

It is not entirely clear why there has been an increase in high-grade abnormality detection (which, as noted below, is primarily due to a modest increase in detection for women aged 25–39), and there may be various contributing factors. Some of these may be related to a change in classification of abnormalities as a result of the change in guidelines (for instance if a pathologist is unsure whether an abnormality should be classified as low-grade or high-grade, they may be more inclined to classify it as a high-grade under the new Guidelines because high grade abnormalities are monitored more conservatively).

The SMC noted this increase in high-grade abnormalities, and gave due consideration to its implications. The view of the SMC is that, although it was not entirely clear why there had been an increase in high-grade abnormalities, the change in management guidelines could not be excluded as a cause. It was reassuring that this increase was not accompanied by an increase in cervical cancer incidence, which was the key outcome parameter for SMC monitoring.

2.4 Cervical cancer incidence

Incidence of cervical cancer in 2009

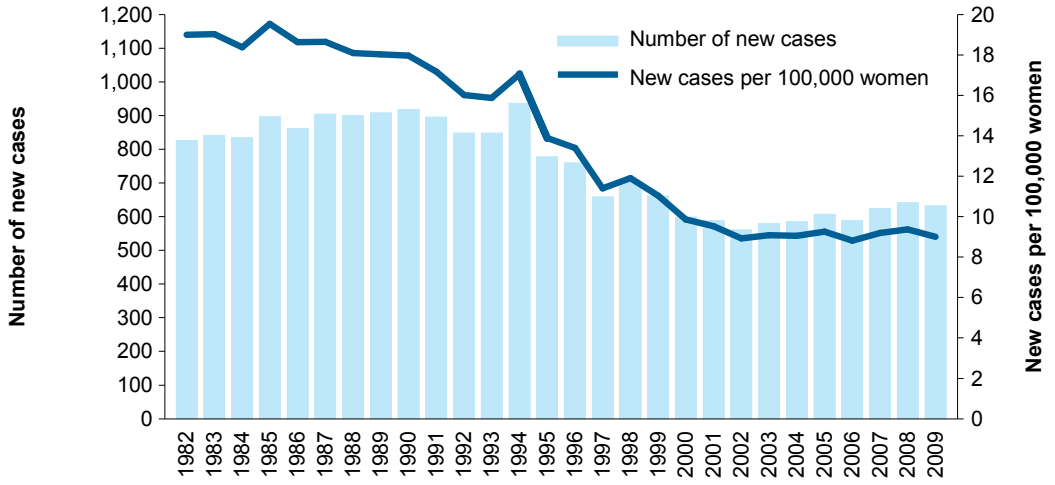
In 2009, there were 771 new cases of cervical cancer in Australian women. This is equivalent to 7 new cases for every 100,000 women in the population. Of these 771 new cases, 631 were in women aged 20–69, the target population of the NCSP.

In the broader context of cancers diagnosed in Australian women (and excluding basal cell and squamous cell carcinoma of the skin), cervical cancer was the 12th most commonly diagnosed cancer in Australian women in 2009, and comprised 1.5% of all cancers diagnosed in women (AIHW & AACR 2012). The mean age at diagnosis of cervical cancer was 50.2 years, and the risk of diagnosis with cervical cancer was 1 in 198 by age 75 years and 1 in 162 by age 85 (AIHW & AACR 2012).

Incidence of cervical cancer trends

While incidence had been slowly decreasing before the organised national screening program, the decrease accelerated after the establishment of the program. Since then the incidence has almost halved between 1991 and 2009 from 17.2 to 9.0 new cases per 100,000 women (a decrease in the number of new cases from 895 to 631) for women aged 20–69 (Figure 2.4).

Since an historic low in 2002, rates have remained relatively stable at 9 new cases per 100,000 women (Figure 2.4).



Note: Rates shown are the number of new cases of cervical cancer per 100,000 women, age-standardised to the Australian population at 30 June 2001.

Source: AIHW 2013.

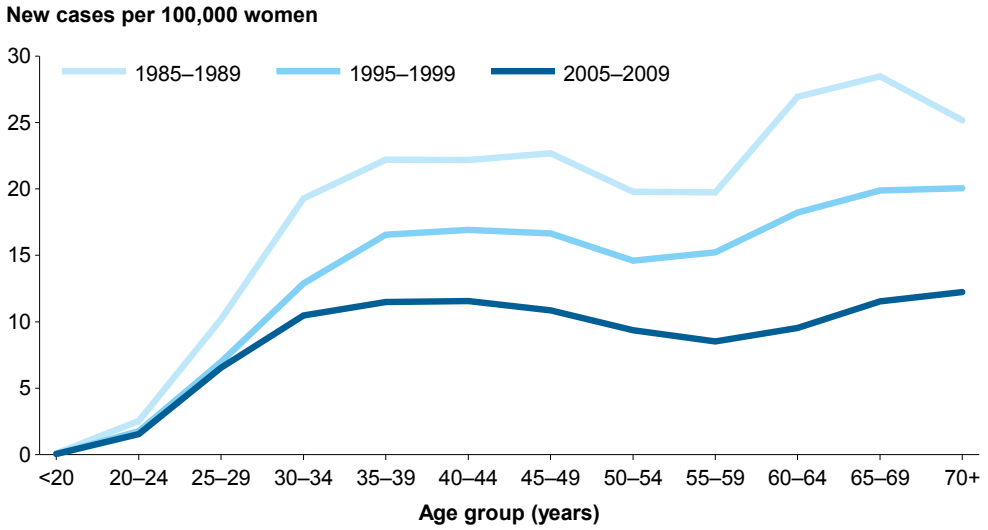
Figure 2.4: Incidence of cervical cancer in women aged 20–69, by year, 1982 to 2009

Incidence of cervical cancer trends beyond 2009

The Victorian, Queensland, Western Australian, South Australian and Tasmanian cancer registries were able to assist by providing the SMC with cervical cancer incidence data for 2010 and 2011. The AIHW analysed these data for the SMC.

Incidence rates for 2010 and 2011 in these five states did not vary outside the range observed in the previous 5 years. The data indicated that the stable rate for the country as a whole in 2002–2009 was continuing, at least in these five states.

Incidence of cervical cancer by age



Note: The number of new cases of cervical cancer per 100,000 women are shown for each 5-year age group (crude rates only).

Source: AIHW 2013.

Figure 2.5: Incidence of cervical cancer in women, by age, 1985–1989, 1995–1999 and 2005–2009

Historical age-specific trends reveal the effect of the cervical screening program on incidence. Calculated over 5-year periods to increase stability and comparability of rates, age-specific incidence is shown for 1985–1989, 1995–1999 and 2005–2009 in Figure 2.5.

It is evident that incidence decreased across all age groups from 1985–1989 to 2005–2009. Further, in 1985–1989, before the NCSP was introduced, there was a clear second (and higher) peak in incidence in women aged 60 onwards, which has since fallen (Figure 2.5).

Incidence by histological type

Table 2.4: Incidence of cervical cancer in women aged 20–69, by histological type, 2008

Type of cervical cancer	New cases	AS rate	% of cervical cancers	(% of carcinomas)
1: Carcinoma	630	9.2	98.3	(100.0)
1.1: Squamous cell carcinoma	419	6.1	65.4	(66.5)
1.2: Adenocarcinoma	164	2.4	25.6	(26.0)
1.3: Adenosquamous carcinoma	21	0.3	3.3	(3.3)
1.4: Other specified and unspecified carcinoma	26	0.4	4.1	(4.1)
2: Sarcoma	3	0.0	0.5	. .
3: Other specified and unspecified malignant neoplasm	8	0.1	1.2	. .
Total	**641**	**9.4**	**100.0**	**. .**

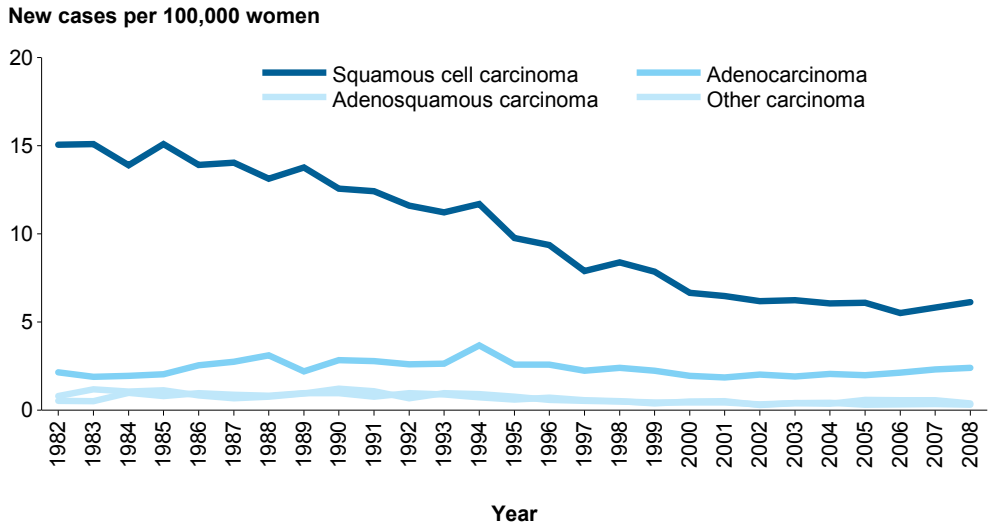
Note: Age-standardised (AS) rate is the number of new cases per 100,000 women, age-standardised to the Australian population at 30 June 2001; rates based on less than 20 new cases should be interpreted with caution. Per cents shown are crude only.

Source: AIHW Australian Cancer Database.

In 2008, of the 641 cervical cancers diagnosed in women aged 20–69, 630 (98.3%) were carcinomas, 3 (0.5%) were sarcomas, and 8 (1.2%) were classified as other and unspecified malignant neoplasms (Table 2.4). Of the 630 carcinomas diagnosed, squamous cell carcinoma

comprised the greatest proportion at 66.5%, followed by adenocarcinoma at 26.0%, and adenosquamous carcinoma at 3.3% in women aged 20–69 (Table 2.4).

Trends in age-standardised incidence rates for women aged 20–69 between 1982 and 2008 for squamous cell carcinoma, adenocarcinoma, adenosquamous carcinoma and other carcinomas are shown in Figure 2.6.



Note: The number of new cases of squamous cell carcinoma, adenocarcinoma, adenosquamous carcinoma, and other carcinoma of the cervix, are shown per 100,000 women, age-standardised to the Australian population at 30 June 2001.

Source: AIHW Australian Cancer Database.

Figure 2.6: Incidence of carcinoma of the cervix (squamous cell carcinoma, adenocarcinoma, adenosquamous carcinoma and other carcinoma) in women aged 20–69, by year, 1982 to 2008

3 Outcomes of projects to assess the safety of the guidelines

3.1 Are women with a pre-invasive cervical abnormality more likely to be diagnosed with a subsequent cervical cancer since the introduction of the guidelines?

The primary analyses that the SMC considered involved comparing the occurrence of cervical cancer after an abnormality following the guideline change with the occurrence beforehand. Specifically, occurrences of cervical cancer following a low-grade squamous abnormality detected by cytology, or a high-grade abnormality detected by histology, were compared across these periods since they were relevant to the two major changes to the guidelines.

Reassuringly, there was no overall increase in cervical cancers found following detection of these abnormalities in women managed under the new NHMRC Guidelines compared with that which applied under the previous NHMRC Guidelines.

Detailed findings are presented for cervical cancer after a low-grade squamous abnormality detected by cytology, since this analysis includes an adequate number of cancers and time elapsed per person for meaningful conclusions.

No overall increase in cervical cancer was found after detection of pre-invasive abnormalities in women managed under the new NHMRC Guidelines when compared with numbers of cervical cancers after pre-invasive abnormalities in women managed under the previous NHMRC Guidelines.

While brief results are presented for an interim analysis that looks at cervical cancer after a high-grade abnormality detected by histology, and early findings of women who have completed test of cure are also given, neither of these analyses had adequate data to provide definitive results.

Methodology

The following methodology, endorsed by the SMC, compares the incidence of cervical cancer after a Pap test result of possible or definite low-grade squamous intraepithelial lesion, or a high-grade histology result, in women managed under the 1994 guidelines compared to those managed under the 2005 guidelines.

The AIHW undertook these analyses for the SMC.

Aim: To compare the incidence of cervical cancer after a low-grade squamous cytology result before and after the introduction of the 2005 NHMRC Guidelines.

Data source and parameters

All data were supplied by the state and territory cervical cytology registers, with the exception of South Australia, which is excluded from the analyses in this report due to data not being available at this time. The Chief Health Officer in each state and territory and the AIHW Ethics Committee approved the supply and use of these data.

Data for women managed under the 1994 guidelines (referred to as 'baseline') were collected from 1 January 1999 to 30 June 2006, with data analysed from 1 January 2001 to 30 June 2006.

Data for women managed under the 2005 guidelines (referred to as 'ongoing') were collected from 1 July 2006, with data analysed from 1 January 2007 to 30 June 2012, allowing a 6-month 'wash out' period after the introduction of the 2005 guidelines (as inclusion of this period could potentially include women with mixed investigation and management).

Only women aged 20–69 (the target age group of the NCSP) are included in analyses.

Cohort design

Women enter the cohort with a Pap test result of possible or definite low-grade squamous intraepithelial lesion in either the baseline or ongoing time periods. Their progress is measured until they are either diagnosed with cervical cancer or leave the cohort either at the end of follow-up (2 or 5 years) or through censoring at the end of the observation period (see Box 3) or due to death. Women who have previously had histologically confirmed high-grade disease or a diagnosis of cervical cancer are excluded from entering the cohort.

Box 3.1: Statistical terminology

In a cohort design, there is usually an end-point to the study, on which date all people who are still in the cohort (that is, have not been censored (stopped) for another reason prior to this date) are censored due to 'end of **observation period**'. In these data, the end-point of the baseline data is the 30 June 2006 (just prior to the introduction of the new guidelines), and the end-point of the ongoing data is 30 June 2012 (to reflect the end-point of the data supplied).

This study also uses a defined **follow-up period**, by which women are censored after 2 years if they have not previously been censored for another reason.

Person-time, in years, is calculated by measuring the time from each woman's entry into the cohort until they are either diagnosed with cancer or leave the cohort (at the end of follow-up or through censoring at the end of the observation period or due to death).

Table 3.1 describes the selection of women for inclusion in the baseline and ongoing cohorts.

Table 3.1: Number of low-grade squamous cytology tests, women aged 20–69, baseline and ongoing cohorts

	Baseline	Ongoing
Low-grade squamous cytology in women aged 20–69	541,711	442,846
Exclusion of women with previous histologically confirmed high-grade disease	512,685	411,286
Exclusion of women with previous cervical cancer diagnosis	512,413	411,073
Removal of duplicate cytology tests (number of women in cohort)	512,315	411,041

Note: Baseline is 1 January 2001 to 30 June 2006; ongoing is 1 January 2007 to 30 June 2012.

Source: AIHW analysis of state and territory cervical cytology register data.

Statistical analyses

Proportional hazards regression was used to estimate the hazard ratio (with 95% confidence intervals (CI)) for an increase or decrease in cancer incidence in the ongoing cohort relative to the baseline cohort (see Appendix D).

A Z-score (a function of the proportional hazards estimate and its standard error) for each 6-month monitoring point was placed into the context of safety monitoring boundaries set by the methodology, whereby a warning flag is raised if the hazard ratio increased and this exceeds the 10% α-level, and an immediate action required flag is raised if this exceeds the 5% α-level. Due to the sequential nature of the monitoring process, adjustment was made for multiple testing (Wang & Tsiatis 1987).

Cumulative incidence curves, were calculated for baseline and ongoing incidence over the 2-year follow-up period (more information is provided in Appendix D).

Results

The proportional hazard ratio calculated between the baseline and ongoing cohorts, with 2 years follow-up, was 0.94 (95% CI 0.73–1.19). This is not statistically significantly different to 1, indicating no statistically significant change in the risk of cancer after a low-grade squamous cytology under the new guidelines compared to the previous guidelines.

There was no statistically significant change in the risk of cancer after a low-grade squamous cytology under the new NHMRC Guidelines compared to the previous guidelines.

The proportional hazard ratio was also calculated with 5 years follow-up. These data are shown in Table 3.2, below.

Table 3.2: Summary of low-grade cohort data, baseline and ongoing, 2 and 5 years follow-up

	Baseline	Ongoing	Hazard ratio
2 years follow-up			
Low-grade abnormalities	512,315	411,041	0.94
Total person-time in cohort (years)	680,683	579,058	(0.74–1.19)
Cancers in cohort	158	119	
5 years follow-up			
Low-grade abnormalities	512,315	411,041	1.03
Total person-time in cohort (years)	1,042,976	918,151	(0.83–1.27)
Cancers in cohort	188	159	

Note: Baseline is 1 January 2001 to 30 June 2006; ongoing is 1 January 2007 to 30 June 2012.

Source: AIHW analysis of state and territory cervical cytology register data.

The proportional hazards model was adjusted for the potential confounders of year and age (with age centred around age 50), but this did not have a significant effect on model results.

Monitoring checkpoints and their respective critical values are shown in Table 3.3, as are the hazard ratio, Z-score and action for each of the eight monitoring checkpoints completed. As shown in Figure 3.1, the adjusted hazard ratio estimates for low-grade cytology for all of the monitoring checkpoints are well within the critical values set for these respective checkpoints.

Table 3.3: Critical values calculated for monitoring checkpoints

Monitoring checkpoint	Observation period ending	Hazard ratio	Z-score (test statistic)	Critical values for warning flag (exceeds 10% α-level)	Critical values for immediate action flag (exceeds 5% α-level)	Action
1	December 2008	1.24	0.61	3.20	3.67	Continue
2	June 2009	1.08	0.49	2.69	3.08	Continue
3	December 2009	1.01	0.07	2.43	2.79	Continue
4	June 2010	1.08	0.57	2.26	2.59	Continue
5	December 2010	1.06	0.45	2.14	2.45	Continue
6	June 2011	0.99	−0.08	2.05	2.34	Continue
7	December 2011	0.95	−0.41	1.97	2.25	Continue
8	June 2012	0.94	−0.51	1.90	2.18	None required

Note: Critical values for monitoring test checkpoints were calculated based on Wang & Tsiatis (1987).

Source: AIHW analysis of state and territory cervical cytology register data.

The SMC was required to raise a warning flag if the incidence was increased and the test score exceeded the 10% α-level, and to raise an immediate action required flag if this score exceeded the 5% α-level.

The safety monitoring boundaries are illustrated in Figure 3.1.

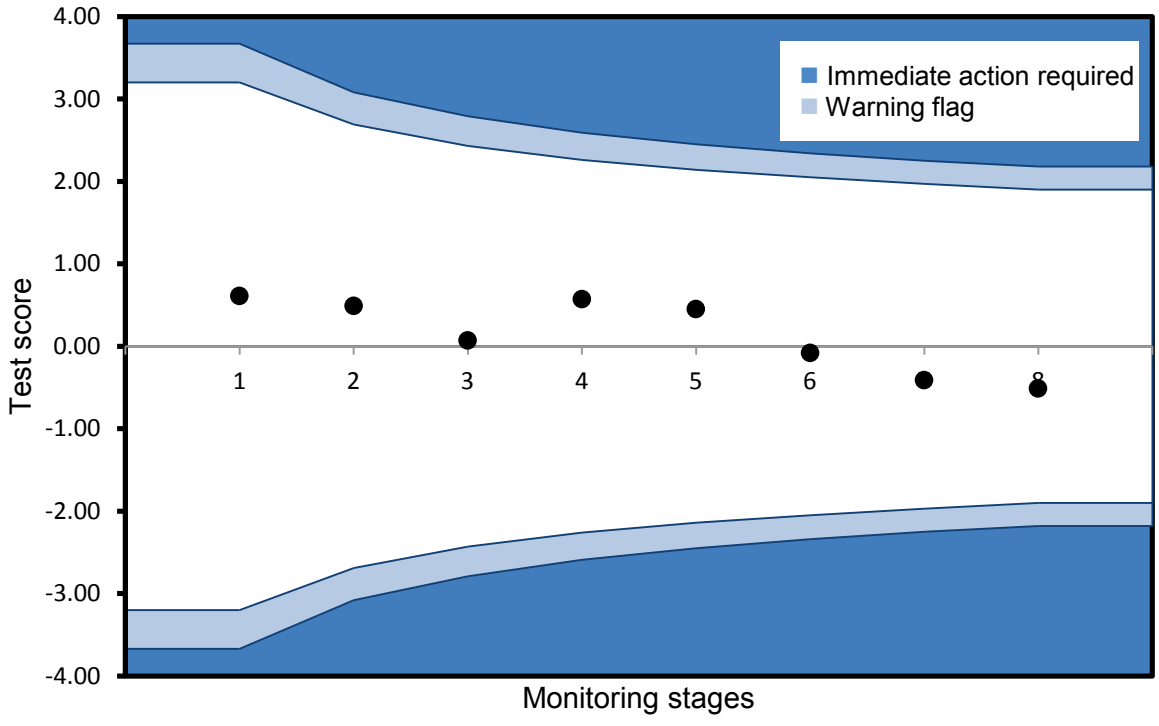


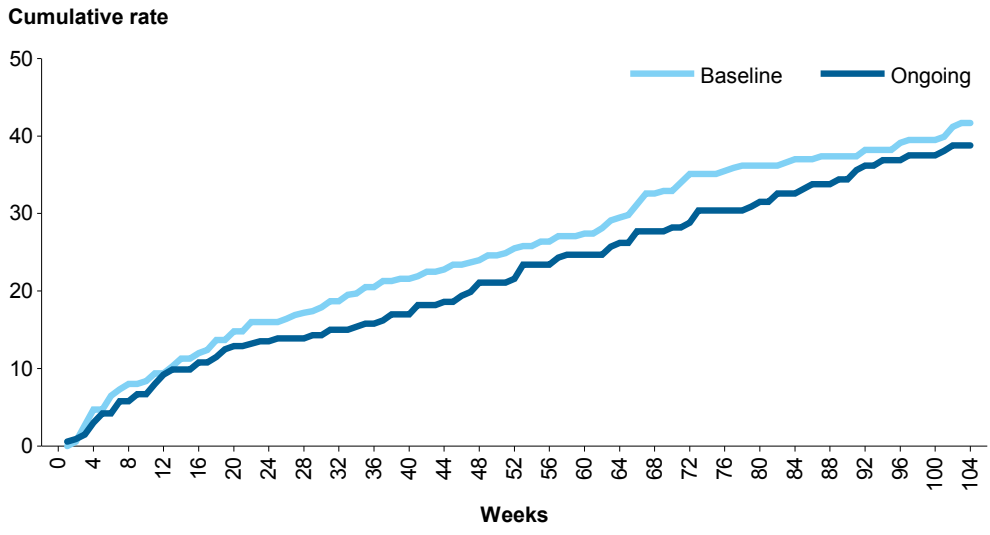
Figure 3.1 Boundaries for adjusted hazard ratio

The critical values are described in the tables and illustrated in the figures. The funnel shape of the boundary plot illustrates the critical values decreasing with each monitoring point (set at the end of each observation period). The horizontal axis represents each of the monitoring points and the vertical axis represents the test score and critical values at each checkpoint. The test statistic is denoted by a black circular symbol.

The approach was that, if the test score exceeded the critical values generated from the sequential design, appropriate action would be taken, otherwise monitoring would continue. The SMC was required to raise a warning flag if the test score exceeded the 10% α-level, and to raise an immediate action required flag if this exceeded the 5% α-level.

Cumulative incidence curves are based on the Kaplan-Meier product limit method of time to event estimation. Kaplan-Meier methods are standard methods used to estimate the frequency distribution (or incidence curve) of an event over time (see Appendix D). In this case it was the time, measured in weeks, to a cervical cancer diagnosis following the identification of either a low-grade cytology abnormality or a high-grade histology abnormality.

Figure 3.2 shows the Kaplan-Meier cumulative cervical cancer incidence curves over 2 years (104 weeks) of follow-up for baseline and ongoing cohorts. This shows the time, measured in weeks, to a cervical cancer diagnosis following a low-grade cytology abnormality. Again, no increase in incidence of cervical cancer was observed following the introduction of the new guidelines.



Source: AIHW analysis of state and territory cervical cytology register data.

Figure 3.2: Cumulative rate of cervical cancer by time in cohort, baseline and ongoing

Additional results for high-grade abnormalities

In addition to the previously described analyses of incidence of cervical cancer after a low-grade squamous cytology, two additional analyses were undertaken to look at incidence of cervical cancer after a histologically confirmed high-grade abnormality.

Under the previous guidelines, women treated for a histologically confirmed high-grade abnormality were advised to continue with annual Pap tests *ad infinitum*. Under the new guidelines, women treated for a histologically confirmed high-grade abnormality are eligible

to undergo a 'test of cure'. A test of cure involves a cytology test and an HPV DNA test around 12 months after the completion of treatment, followed by another cytology test together with another HPV DNA test 12 months later. If both sets of cytology and HPV DNA tests are negative, then a woman is deemed to have completed her test of cure, and can return to regular 2-yearly cervical screening. This is the screening interval currently recommended for women who have no symptoms or history suggestive of cervical pathology.

The first analysis was an interim measure looking at cervical cancer incidence in the 2 years following a histology result of high-grade abnormality. As there are no management changes between the previous guidelines and the new guidelines for this period, this analysis does not address the safety of new management practices. This interim assessment was undertaken in the interests of monitoring the whole screening pathway and in advance of sufficient data arising to allow assessment of cervical cancer incidence after a completed 'test of cure' and return to routine 2-yearly screening.

A comparison of cervical cancers that occurred in the 2 years following a 12-month clinical management period immediately following a histologically confirmed high-grade abnormality was made. The numbers were small with 22 cancers found for the baseline period and 36 following introduction of the new guidelines. Proportional hazards regression did not reveal this to be a statistically significant increase and the 10% α-level was not reached to raise an alert.

A comparison of the cervical cancers that occurred following a histologically confirmed high-grade abnormality between the two guidelines did not raise a warning flag at the 10% α-level.

It should be reiterated that in the period of time so far studied after high-grade abnormalities were detected by histology for this interim measure, there had been no change in the management. Accordingly, even if a statistically significant increase had been found, it would not have related to a change in NHMRC Guidelines. It is planned that, as a further check, numbers of cervical cancers occurring after high-grade histology will continue to be monitored to gain more definitive results.

The second analysis assessed cervical cancer incidence after women had completed 'test of cure'. Under the new guidelines, unless both sets of cytology and HPV DNA tests are negative, a woman has not completed her test of cure, and is recommended that she has a cytology test and an HPV DNA test every 12 months until she achieves two consecutive negative cytology and HPV DNA tests 12 months apart. Completing the 'test of cure' represents a change from the previous guidelines that recommended annual cervical screening *ad infinitum* following treatment of a high-grade histological abnormality.

Due to the time required after high-grade diagnosis to complete treatment, undergo and eventually complete test of cure, and be returned to routine 2-yearly screening, there are at present only limited data available on cancer outcomes for these women. The present data include women aged 20–69 with no prior history of cervical cancer with histologically confirmed CIN II or CIN III diagnosed since 1 January 2007, with consecutive negative cytology and HPV DNA test results at least 10 months apart (10 months was used instead of 12 months to allow for women who were tested earlier).

Using this methodology, only 4,360 women were identified who had completed test of cure with the limited amount of follow-up data available. Importantly, there were no cervical cancers diagnosed in any of these 4,360 women who had completed their test of cure.

There were no cervical cancers diagnosed in any of the 4,360 women who had completed their 'test of cure'.

Cervical cancer incidence after completion of test of cure will continue to be monitored, and should provide more definitive findings as more follow-up data become available.

3.3 What did the review of cervical cancer cases included in the analyses reveal?

A review of the screening histories of women diagnosed with cancer was recognised as a key component of safety monitoring for the new guidelines. A cancer audit is an important tool to monitor program effectiveness and identify areas where improvements to the program can be made. A number of countries have commenced comprehensive audits of their cervical screening programs, in particular New Zealand and the United Kingdom.

Aim: To conduct a qualitative review of cancers arising in the study cohorts.

The primary goal of this audit was to conduct a qualitative review of cancers arising in the study cohorts, providing an additional perspective to the statistical analysis being conducted as part of the safety monitoring of the NHMRC Guidelines. The scope of this audit is limited to a qualitative review of de-identified data that the AIHW had received from the cervical cytology registers for the purpose of safety monitoring. Specifically it was outside the scope of this audit to review medical records or histology slides or seek information from treating medical practitioners.

Methodology

Relevant data on screening histories were supplied to the AIHW from cervical cytology registers for women with an index Pap test result with a low-grade squamous abnormality who had a cancer diagnosed within 5 years of the low-grade cytology result. Both censored cancers and cancer 'events' in the main analysis were reviewed as part of this audit.

Data from women in periods of observation both before and after the introduction of the new guidelines were reviewed as there were no major differences in coding that would affect the interpretation of the data.

The audit relates to the cohort of women included in the monitoring of the NHMRC Guidelines described above. It should be noted that this audit is not representative of the majority of cervical cancers that occur in Australian women who have a poor screening history or who have never been screened.

To assist in interpretation, the cancer cases have been classified into broad categories based on how closely NHMRC management guidelines had been followed, based on the data available. This process was dependent on the available screening histories and no definitive classification can be made in the absence of colposcopy and treatment data.

A small group within the SMC undertook these analyses specifically for the SMC. The group included representatives from the AIHW, the Victorian Cervical Cytology Registry, and the Australian Society of Colposcopy and Cervical Pathology. The state and territory cervical cytology registers supplied all data. The Chief Health Officer in each state and territory and the AIHW Ethics Committee approved the supply and use of these data.

Limitations of data

There are a number of important limitations to consider when interpreting the findings of this audit. The available data held by cervical cytology registers were largely limited to the cytology, histology and HPV testing for each woman diagnosed with cancer, supplemented

by the laboratory recommendation codes where they were recorded. Cervical cytology registers do not systematically collect data on treatment or colposcopy and symptom status is not recorded in a nationally consistent manner.

Colposcopy data

The cervical cytology registers operate under the relevant legislation for their state or territory, and receive data on cervical cytology and relevant cervical histology directly from reporting laboratories in a timely manner. However, cervical cytology registers do not receive systematic information on colposcopies performed.

The lack of data on colposcopy precludes an accurate assessment of whether the guidelines were followed, as in most instances a colposcopy was recommended.

Treatment data

The cervical cytology registers do not systematically record information on the treatment of women involved in the screening program. Although information can sometimes be derived from details of the procedure recorded in the histopathology report, it is not always possible to tell what type of treatment was performed, or if a woman was treated at all. In the case of ablative treatment, there may be no associated report if no biological sample was taken.

Symptom status

Symptom status is able to be recorded, which allows women with symptoms who are identified as such at the time of their cervical cytology test to also be identified on the cervical cytology registers. However, the completeness of this field depends on both the clinicians requesting the Pap test and laboratories coding the information appropriately. The proportion of women with symptoms recorded was found to vary too much across states and territories to be regarded as reflecting any genuine differences in women with symptoms. The inconsistent use of the symptom code nationally led to this finding.

Findings of the audit

Low-grade cohort

The screening histories were reviewed in women who developed a cancer following a low-grade cytology result.

Broadly speaking, the cancer review found evidence that the guidelines had been followed in around half of the cervical cytology cases, as there was a record of a subsequent cytological or histological test being performed within the recommended interval.

In the remainder of cases, it was not possible to determine whether the guidelines had been followed as information on colposcopy was unavailable if a biopsy had not been performed. Also, it was not possible to determine occasions when a woman had an early referral due to the presence of symptoms, due to the poor quality of recording of this information.

Interestingly, 69% of cases had not had a negative screening history in the 3 years prior to the index low-grade cytology which entered them into the cohort. This proportion was even higher in women with no prior negative screening history that were diagnosed with cervical cancer within 6 months of the low-grade cytology.

The rate of cancer following a low-grade abnormality in the ongoing cohort was 1 in 1,924 women compared with the baseline cohort rate of 1 in 2,245 women. The review of cervical

cytology registers' data on cancers after low-grade cytology for the ongoing cohort reflected a range of possible reasons for subsequent diagnosis including:

- failure to diagnose the cancer in a timely manner (failure of colposcopy or biopsy)
- inadequate prior screening history
- possible underdiagnosis on cytology
- in some cases, rapid progression of cancer.

Based on the information available, it was not possible to distinguish between these possibilities in many instances and the reasons for diagnosis are likely to be multifactorial.

The cancer case review was also conducted on cancers following women with a histologically confirmed high-grade abnormality, for which detailed results have not been shown in Chapter 3.1. Briefly, it was concluded that very few women had any significant loss to follow-up after a high-grade abnormality, suggesting the registry safety net in Australia is working well. However, as expected, most women had an inadequate screening history prior to cancer diagnosis which may have led to larger lesions that were more difficult to treat. None of the women examined appeared to have completed 'test of cure' at the time the review was conducted.

Discussion

Cancer audits are a useful tool for monitoring the quality of a screening program and identifying areas where improvements can be made. The focus of this review was on cancers arising after a screen-detected abnormality which represented only a proportion of cervical cancers diagnosed in Australia, since the majority of these cancers occur in unscreened or underscreened women.

Overall, the cancer audit provides descriptive data to support the quantitative analysis being undertaken; however, it is limited because cervical cytology registers do not systematically collect data on colposcopy and treatment. Symptom status was also not recorded in the vast majority of cases in the study cohort. Given the data available for the review, the SMC concluded that a range of factors may have contributed to the cancers arising, following on from the detection of cytological abnormalities.

3.4 What did the survey of pathology laboratories reporting cervical cytology show?

Pathology laboratories have a central role in the National Cervical Screening Program. More than 2 million cytology tests are collected and reviewed in Australian pathology laboratories each year. High-quality cervical cytology is a key component of the assessment and treatment of women with abnormalities that are a precursor to cervical cancer.

Aim: To seek feedback from laboratories on the processes used to make recommendations for women with screen-detected cervical abnormalities.

As part of a wider range of activities that the Safety Monitoring Committee (SMC) undertook, the committee sought feedback from laboratories on the processes used to make recommendations for women with screen-detected cervical abnormalities. With the assistance of the Royal College of Pathologists of Australasia (RCPA) Cytopathology Quality Assurance Program. A survey to assess reporting systems of pathology laboratories was distributed to 51 pathology laboratories that report cervical cytology. The responses from laboratories that returned the survey to the Department of Health are included in the analysis below.

The survey received a response from 32 cytological laboratories, a participation rate of around 63%. New South Wales had the highest number of respondents (11 laboratories) followed by Western Australia and Victoria. There were no respondents from South Australia or the Northern Territory. Three-quarters of the laboratory services were found to report to only one cervical cytology register. A number of the larger laboratories (by number of staff), reported to more than one register, suggesting that there may be a correlation between the size of the service and the number of registers to which services report. However, there were exceptions to this pattern.

A small group within the SMC undertook these analyses specifically for the Committee, including representatives from the Royal College of Pathologists of Australiasia and the National Cervical Screening Program Managers.

Reporting cervical cytology results

As described in Box 4 below, cytology laboratories often access information from cervical cytology registers on screening histories when making recommendations on patient management. The survey found the most common method of accessing patient screening histories from cervical cytology registers was through a batch enquiry—that is an electronic request for screening histories for a number of clients (accounting for just under half of the respondents), followed by online enquiry. Three laboratories reported that they did not have timely access to patient histories.

A sizeable proportion (41%) of laboratories indicated that there are situations where no specific recommendation is made on a Pap test result. Additional comments indicated that, in cases dependent on clinical circumstances, recommendations were left to the clinician. That is, in patients with an abnormal smear and with a history of cervical abnormalities but no record on the registry or in patients referred to a gynaecologist or other specialist, recommendations were left to the clinician.

Box 4: Role of pathology laboratories in cervical screening

Pathology laboratories play a major role in cervical screening. A Pap test involves a general practitioner, gynaecologist or reproductive health nurse collecting cells from the cervix and placing them on a glass slide. The slide is then sent to a pathology laboratory where the cells are examined by a cytologist or laboratory technician for abnormal cellular changes. These results are compared with the recorded screening history that the cervical cytology registers provide. Findings are reported back to the clinician along with a recommendation for patient management—the patient may be referred for further tests with a specialist to see if treatment is required. The cytology laboratories also notify the cervical cytology registers, allowing a record of the screening history to be established and maintained.

High-quality cervical cytology in Australian pathology laboratories has been a key component of the cervical screening program, facilitated through the development of National Pathology Accreditation Advisory Council (NPAAC) *Performance measures for Australian laboratories reporting cervical cytology* (NPAAC 2006a).

To understand how laboratories have integrated recommendations made in the NHMRC Guidelines in the preparation of cervical cytology reports, the laboratory services were asked whether they used an automated system using an algorithm based on the 2005 NHMRC Guidelines in making recommendations for cervical cytology reports.

Manual systems outnumbered automated decision support systems with a majority of responding laboratories (62.5%) indicating that they were not using automated systems. The survey found that manual methods for entering results are still common, especially in the laboratories with a small number of employees.

Reporting of symptom status

Women who have symptoms that could indicate the presence of cervical cancer (such as abnormal bleeding) at the time of their cytology test are advised to be referred for further investigation and diagnostic testing, as the guidelines only cover asymptomatic women.

In the National Cervical Cytology Coding Sheet introduced in July 2006, recommendation codes included the code RS *Symptomatic-Clinical management required* which allows women with symptoms who are identified as such at the time of their cervical cytology test to be identified on the cervical cytology registers. Symptom status provides useful additional clinical information for women on the register, and can alter the management recommended for these women.

The majority of laboratories (81.3%) indicated that they had strategies in place for reporting Pap tests in patients with symptoms reported on the request form. Some of these strategies included modifying the standard comments or referral to a specialist. There was broad agreement on the types of symptoms that would lead to the laboratory to recommending *Symptomatic-Clinical management* on a Pap test result. When grouped together these symptoms tended to fall into three broad groups, most commonly 'Abnormal or irregular bleeding' (which included post-coital bleeding or post-menopausal bleeding), 'Suspicious or abnormal Cervix' and 'Abnormal smear/other types of Clinical information'.

Although there appeared to be broad agreement between laboratories in the manner of describing symptom status across states and territories, use of the RS code was found to vary between 0.02% and 2.38% in 2008–2009 (AIHW 2011). This variation was considered to be too large to be attributable to differences in women's symptom status and was attributed to

inconsistent use of the symptom code nationally. It is not clear at what stage of the process this inconsistency lies and further investigation is required to increase the completeness of the symptom field.

Cytology labour force

The laboratories were questioned about the number and make-up of scientific staff within the laboratory (see Box 5). Qualified scientists outnumbered pathologists in nearly all of the laboratories, averaging 8.7 full-time equivalent (FTE) scientists compared with 3.5 FTE pathologists. There were low numbers of current trainees among the responding laboratories with an average of 0.5 FTE across all laboratories.

While just over two-thirds (68.8%) of laboratories participating in the survey expressed a willingness to train new scientific staff, indicating that they currently train or have previously trained new staff, just over three in ten (31%) currently had a trainee. This rate was slightly higher (40%) in laboratories with more than ten employees. Common reasons for not conducting training included a lack of graduates with specific cytology qualifications to do the training; a view that there was no need to train new recruits due to a stable workforce; or the limited size and resources of the laboratory being regarded as insufficient to commit to training.

The preference of most of the surveyed laboratories to recruit scientists or pathologists with formal qualifications in cytology is likely to improve the quality of the program.

Box 5: Pathology laboratory staff

Pathology laboratory staff include pathologists, scientists and cytotechnologists.

A pathologist involved in gynaecological cytology is required to be a Fellow of the Royal College of Pathologists of Australasia (RCPA) or hold an equivalent qualification.

Screening staff must include scientists or cytotechnologists who hold qualifications which designate competence in cytology (scientists are required to have a relevant degree in science or applied science together with a minimum of 2 years full-time training/experience in a National Association of Testing Authorities/RCPA-accredited laboratory for gynaecological cytology, and a senior cytotechnologist is required to have the equivalent of 5 years full-time experience in cytology and to hold a qualification which designates competence in cytology) (NPAAC 2006b).

3.5 What did the compliance study reveal?

There were several changes to the NHMRC Guidelines that affected the formulation of laboratory recommendations for reporting cervical cytology. The aim of the analysis shown in this chapter was to assess the compliance of laboratory recommendation codes with the NHMRC Guidelines in Victoria. Data were examined with the objective of:

- describing the prevalence of laboratory recommendation codes for cervical cytology in Victoria, by year and by reporting laboratory
- comparing laboratory recommendations with the guidelines' recommendation for women who have had low-grade squamous intraepithelial abnormalities on cytology
- comparing laboratory recommendation and the guidelines' recommendation with actual screening interval to determine what proportion of women follow this recommendation.

Aim: To assess the level of compliance of laboratory recommendation codes with the NHMRC Guidelines.

Since the introduction of the Australian standard cervical cytology coding schedule in 2006, all Pap test registers have been collecting information on the laboratory recommendations accompanying Pap test reports.

Table 3.4: Coding for management recommendations on laboratory reports

Recommendation code	Definition
R0	No recommendation
R1	Repeat smear 3 years
R2	Repeat smear 2 years
R3	Repeat smear 12 months
R4	Repeat smear 6 months
R5	Repeat smear 6-12 weeks
R6	Colposcopy/biopsy recommended
R7	Already under gynae management
R8	Referral to specialist
R9	Other management recommended
RS	Symptomatic—clinical management required

Source: National Cervical Cytology Coding Sheet 2006.

In Victoria, about 50% of all Pap tests are conducted at Victorian Cytology Service (VCS) Pathology, which has a decision support tool to assist scientists and pathologists to make recommendations compliant with the NHMRC Guidelines, taking account of the all relevant variables. Therefore it was important to compare recommendations made by VCS Pathology with those of other Victorian laboratories which may not use such a decision support tool for reporting cervical cytology.

Methodology

The prevalence of the recommendation codes that laboratories used was analysed for all cytology results between 1 January 2007 and 31 December 2011.

Concordance of laboratory recommendations and of the observed screening interval with the NHMRC Guidelines was analysed for women who had a low-grade abnormality detected on cytology in the period 1 July 2006 to 31 December 2011. Screening records (back to 1 January 1997) were also retrieved for each of these women, in order to determine the appropriate follow-up management. The 2005 NHMRC Guidelines were used to determine the relevant recommendation codes based on each woman's screening history, age at the time of the cytology test (<30, >=30), and the cytological result category (negative, low-grade squamous abnormalities and high-grade squamous abnormalities).

The actual screening interval was also measured by examining the proportion of women who attended the next test within the interval recommended in the guidelines, as well as those who attended up to 3 months later than the interval recommended by the guidelines. Cumulative incidence figures of screening attendance, stratified by reporting laboratory, were reported.

The University of New South Wales, on behalf of the VCS, performed analyses for the SMC using Victorian Cervical Cytology Register data.

Results

Changes observed in the recommendations made by pathology laboratories for low-grade abnormality test results were consistent with changes to the guidelines recommending a 12-month repeat Pap test unless there is an exception to low-grade management. There had been some variation in the recommendation codes used for possible low-grade test results prior to the implementation of the guidelines which appears to have stabilised since the introduction of the new guidelines.

In general, the concordance of laboratory recommendation codes with guideline recommendations was high for negative smears and for those where the result was a high-grade abnormality or the more serious diagnosis of cervical cancer. Concordance with guideline recommendations was high at all laboratories for low-grade abnormality results where standard management is recommended; that is women with a first low-grade abnormality result who did not fall into the 'exceptions' category. In these cases women are recommended to return at 12 months, and concordance was high in this group (96% for women aged less than 30; 89% for women aged 30 or more).

For women in the low-grade abnormality management exception category (women aged 30 years or more without a negative smear in the last 3 years), the guidelines give the option of either a repeat cytology in 6 months or immediate referral for colposcopy. Overall compliance with the low-grade management exceptions was 69%, however there was a very marked difference when stratified by laboratory (concordance with guidelines 99% at VCS Pathology; 27% at other Victorian laboratories overall).

Generally, non-concordance with the guidelines appears to be due to recommending follow-up of a low-grade abnormality at 12 months when this was not consistent with the guidelines. In particular, this occurred for women with consecutive low-grade test results and for women aged over 30 without a recent negative history (in the latter case, this occurred only in Victorian laboratories other than VCS Pathology).

Most women returned for their next test within 3 months of the interval that the guidelines recommended. Variations between the observed screening behaviour of women and the guidelines were generally explained by the relevant reporting laboratory's recommendation, but not in all cases. Groups where attendance for any test within 3 months of the time

recommended for their follow-up was lowest were women who had two consecutive low-grade abnormalities (63–81%, depending on the time interval between the two consecutive low-grades), women aged less than 30 with an initial low grade result (79%), and women aged over 30 without a recent negative history (77%; though attendance in this last group differed markedly by reporting laboratory and so is likely related to the differing laboratory recommendations given).

Women with an initial low-grade test result are recommended to attend two follow-up visits 12 months apart. Compliance with the first round visit was reasonably high, although women aged less than 30 were less likely to attend than women over 30 (79% versus 90% within 15 months). This was not explained by differences in laboratory recommendations as a laboratory concordance was high for both groups (96% for <30; 89% for >=30). However, among these women who then had a negative Pap test result, compliance with their second round visit was much lower (66% within 15 months). This did not differ by reporting laboratory, nor was it explained by laboratory recommendations, as concordance of laboratory recommendations with the guidelines was high in this group (92%).

Importantly, a high proportion (96%) of women with a cytology result of a possible high-grade abnormality or worse attended a follow-up visit within 6 months of this result, with little variation by reporting laboratory.

Conclusion

Trends in the use of recommendation codes for reporting cytology have changed since 2006 in line with the new guidelines. Overall, use of recommendation codes examined in Victoria is broadly concordant with the guideline recommendations, with two important exceptions. The first relates to laboratory recommendations by Victorian laboratories other than VCS Pathology for women with low-grade abnormalities who are recommended for earlier management under the guidelines ('exceptions'), but are continuing to receive 12-month repeat recommendations. Laboratories were not consistent in their compliance with this aspect of the guidelines. Given this was a controversial aspect of the guidelines and was designed to improve the safety of the new management pathway for women, further investigation of the reasons for this low compliance is recommended (although it is likely there was not decision support software). Similarly, there is lower concordance with the guidelines for women with a second consecutive low-grade abnormality test result, occurring at their first follow-up visit after an initial low-grade abnormality, particularly if women are late in attending their first visit. It would be valuable to determine if these figures are representative of practice in other states and territories and to consider how future compliance with the guidelines can be maximised.

Overall, laboratory recommendation codes were broadly concordant with the changed management guidelines, although concordance was lower for low-grade management exceptions (that is, women aged over 30 and those who had a second low-grade abnormality). The use of automated decision support tools in laboratories that had them assisted them in complying with the new guidelines.

Actual attendance by women for a follow-up test within 3 months of the recommended interval is generally high. An exception is women with a recent low-grade abnormality, whose first follow-up test was negative. Attendance is much lower than that observed after other recommendations to return in 12 months, and is not explained by laboratory recommendations which were generally consistent with the guidelines. It is possible that

women may interpret this recommendation differently after a negative test than they do after an abnormal test result.

4 Discussion

The projects undertaken under the auspices of the National Cervical Screening SMC provide, in aggregate, a picture of the safety of the NHMRC Guidelines for the management of screen-detected abnormalities in asymptomatic women, introduced in Australia in July 2006. This picture of safety, while current in 2013, may require revision if new evidence comes to light in the future. Nonetheless, the overarching message is that, according to the methods currently used to assess the available evidence, the change in the guidelines has not led to an increase in cervical cancer in the 7 years since that change.

Two main changes to the guidelines were the focus of analyses—women with low-grade squamous intraepithelial lesions, and women who undergo 'test of cure' following a treated high-grade abnormality. Both changes were for less conservative management than recommended in previous management guidelines.

Evidence demonstrated that the change in management for women with a low-grade squamous intraepithelial lesion did not lead to an increase in cervical cancer, with a similar rate of cancers in women managed under the previous guidelines to that in women managed under the new guidelines.

Evidence was only indicative for women undergoing test of cure since the change due to the time required for women to be treated for a high-grade abnormality and then complete test of cure. A maximum of 4,360 women had completed test of cure at the time of preparation of this report. Nonetheless it is relevant to note that women who completed the test of cure had a very low rate of subsequent high-grade abnormality, and to date, no woman who has completed test of cure was subsequently diagnosed with cervical cancer. Outcomes for women who have completed test of cure will continue to be monitored, and the summary findings published in the annual monitoring report for the National Cervical Screening Program, *Cervical screening in Australia*.

To support the quantitative analyses, a qualitative analysis was also undertaken in the form of a cancer case review of the screening histories of women who were diagnosed with cervical cancer, having previously had diagnosis of only a low-grade squamous intraepithelial lesion. This exercise revealed that data from cervical cytology registers were insufficient to conduct a comprehensive case review, as registers do not systematically include colposcopy or treatment data. Symptom status was also not recorded in the vast majority of cases in the study cohort. Nonetheless, from the data available for the review, a range of factors are thought to have contributed to the cancers arising after the detection of cytological abnormalities.

The laboratory survey gave insight into the process that the pathology laboratories who report on cervical cytology results have in place to support the new guidelines.

The compliance study conducted on Victorian data was of great importance. This is because the analyses assessing differences in women managed under the previous versus the new guidelines are meaningless if the new guidelines are not adhered to, and women continue to be managed as per the previous guidelines.

Overall, use of recommendation codes was found to be broadly concordant with the guideline recommendations, with two important exceptions. The first related to laboratory recommendations by Victorian laboratories other than VCS Pathology for women with low-grade abnormalities who were recommended for a repeat Pap test at 6 months or a

colposcopy under the guidelines, but were continuing to receive 12-month repeat recommendations. Given this was a controversial aspect of the guidelines and was designed to improve the safety of the new management pathway for women, further investigation of the reasons for this low compliance is recommended. Similarly, there was lower concordance with the guidelines for women with a second consecutive low-grade abnormality test result, occurring at their first follow-up visit after an initial low-grade abnormality, particularly where women were late in attending their first visit. It would be valuable to determine if these figures are representative of practice in other states and territories and to consider how future compliance with the guidelines can be maximised.

Actual attendance by women for a follow-up test within 3 months of the recommended interval is generally high. There appears to be some difference by age in attendance for the first follow-up test, as women aged less than 30 were less likely to attend within 15 months of their initial low-grade abnormality than women over 30 (even after excluding the subgroup of women aged 30 or more who were recommended for earlier follow-up under the guidelines). This was not explained by differences in laboratory recommendations for the different age groups. Attendance was also much lower among women with a recent low-grade abnormality, whose first follow-up test was negative. Attendance was much lower than that observed after other recommendations to return in 12 months, and this was not explained by laboratory recommendations. It is possible that women may interpret this recommendation differently after a negative test than they do after an abnormal test result.

Overall, laboratory recommendation codes were broadly concordant with the changed management guidelines, although concordance was lower for low-grade management exceptions (that is, women over 30 and those who had a second low-grade abnormality). Evidence showed that the use of automated decision support tools had assisted laboratories in complying with the new guidelines.

This report highlights the importance of monitoring the safety of newly introduced guidelines and of having a strong evidence base to assess this. The changes made to the NHMRC Guidelines were based on such evidence, but it is not always possible to predict what will happen once changes are implemented in a 'real-world' environment. It is also possible that evidence current at one point in time may no longer be relevant, due to the changing nature of the cervical screening environment. Thus it has been critical that safety monitoring of key changes to the guidelines continued over a sufficient length of time to adequately assure the Safety Monitoring Committee that the available evidence was sound, and to be confident in the conclusions drawn from this evidence.

The AIHW supports monitoring of cervical screening data through performance indicators published annually in *Cervical screening in Australia* reports. Some continuing measures of safety monitoring will be included in these reports from 2011–2012 onwards. These measures will monitor the safety of women with a low-grade squamous intraepithelial lesion detection on cytology, and the safety of women who have completed 'test of cure'. If at any time in the future it becomes apparent that the safety of women is in doubt, timely evidence will exist to inform clinicians, policy makers and other key stakeholders, and direct future changes to best clinical practice in the prevention of cervical cancer in Australia.

Appendix A Additional tables

Table A.1: Incidence of cervical cancer, 1982 to 2009

	New cases		AS rate	
Year of diagnosis	20–69	All ages	20–69	All ages
1982	826	963	19.0	14.2
1983	841	994	19.0	14.3
1984	834	1007	18.4	14.2
1985	896	1058	19.5	14.6
1986	861	1019	18.6	13.9
1987	904	1098	18.6	14.4
1988	900	1065	18.1	13.6
1989	908	1072	18.0	13.5
1990	918	1088	18.0	13.5
1991	895	1094	17.2	13.3
1992	848	1027	16.0	12.2
1993	848	1016	15.9	11.9
1994	936	1143	17.0	13.1
1995	777	962	13.9	10.7
1996	759	939	13.4	10.3
1997	658	809	11.4	8.7
1998	701	873	11.9	9.2
1999	661	800	11.0	8.3
2000	598	769	9.9	7.8
2001	588	742	9.5	7.4
2002	560	691	8.9	6.8
2003	579	730	9.1	7.1
2004	585	727	9.1	6.9
2005	607	737	9.3	6.9
2006	588	719	8.8	6.7
2007	624	752	9.2	6.9
2008	641	780	9.3	7.0
2009	631	771	8.9	6.7

Note: Age-standardised rate is the number of new cases of cervical cancer per 100,000 women, age-standardised to the Australian population at 30 June 2001.

Source: AIHW 2013.

Table A.2: Incidence of carcinoma of the cervix (squamous cell carcinoma, adenocarcinoma, adenosquamous carcinoma and other carcinoma) in women aged 20–69, 1982 to 2008

	New cases				AS rate			
Year of diagnosis	SSC[(a)]	AC[(b)]	ASC[(c)]	Other[(d)]	SSC[(a)]	AC[(b)]	ASC[(c)]	Other[(d)]
1982	656	92	22	35	15.1	2.1	0.5	0.8
1983	662	83	23	56	15.1	1.9	0.5	1.2
1984	632	87	44	49	13.9	1.9	1.0	1.1
1985	689	95	35	54	15.1	2.0	0.8	1.1
1986	645	117	42	40	13.9	2.5	1.0	0.8
1987	682	132	41	33	14.0	2.7	0.9	0.7
1988	651	156	40	40	13.1	3.1	0.8	0.8
1989	691	111	50	48	13.8	2.2	1.0	0.9
1990	642	146	49	62	12.6	2.8	1.0	1.2
1991	647	144	41	56	12.4	2.8	0.8	1.1
1992	615	137	50	37	11.6	2.6	1.0	0.7
1993	595	143	48	52	11.2	2.6	0.9	1.0
1994	640	203	40	49	11.7	3.7	0.7	0.9
1995	545	146	34	42	9.8	2.6	0.6	0.8
1996	529	148	40	33	9.4	2.6	0.7	0.6
1997	454	130	33	31	7.9	2.2	0.6	0.5
1998	493	141	30	29	8.4	2.4	0.5	0.5
1999	470	134	23	26	7.9	2.2	0.4	0.4
2000	403	118	30	27	6.7	1.9	0.5	0.4
2001	400	115	32	27	6.5	1.9	0.5	0.4
2002	388	126	18	21	6.2	2.0	0.3	0.3
2003	397	121	25	26	6.2	1.9	0.4	0.4
2004	392	133	27	23	6.1	2.1	0.4	0.4
2005	399	131	20	39	6.1	2.0	0.3	0.6
2006	366	142	22	38	5.5	2.1	0.3	0.6
2007	394	157	24	38	5.8	2.3	0.4	0.6
2008	419	164	21	26	6.1	2.4	0.3	0.4

(a) SSC = squamous cell carcinoma.

(b) AC = adenocarcinoma.

(c) ASC = adenosquamous carcinoma.

(d) Other = other and unspecified carcinoma.

Note: Age-standardised (AS) rate is the number of new cases of squamous cell carcinoma, adenocarcinoma, adenosquamous carcinoma and other carcinomas per 100,000 women, age-standardised to the Australian population at 30 June 2001; rates based on less than 20 new cases should be interpreted with caution.

Source: AIHW 2013.

Appendix B Data sources

Data sources

Data used in this report are derived from multiple sources and are summarised below.

Table B.1: Data sources for projects included in this report

Project	Data source
Background trends in cervical abnormalities and cancer	*Cervical screening in Australia 2010–2011* (AIHW 2013) State and territory cancer registers
Risk of cervical cancer in women with low-grade cervical cytology	State and territory cervical cytology registers
Outcomes in women who have attempted 'test of cure'	State and territory cervical cytology registers
Cervical cancer case review	State and territory cervical cytology registers
Laboratory survey	Pathology laboratories
Compliance study	Victorian cervical cytology register

Appendix C Data quality statement: Cervical screening safety monitoring data

Summary of key issues

- All states and territories maintain a population-based cervical cytology register (also referred to as 'Pap test registers' or 'Pap smear registers') to which all cervical cytology, histology, and human papillomavirus (HPV) DNA tests are reported.
- State and territory cervical cytology registers were established to support the National Cervical Screening Program (NCSP) that commenced in 1991.
- The AIHW receives unit record level cervical screening safety monitoring data from state and territory cervical cytology registers to allow safety monitoring analyses.
- Some duplication may occur where the same test data are reported to the cervical cytology register in two or more jurisdictions. The AIHW is unable to identify or resolve these instances, and the level of duplication is unknown, but believed to be small.
- Cervical cytology databases change every day, adding new records and improving the quality of existing records as new information becomes available.

Description

All states and territories have legislation that requires pathology laboratories to send a copy of all cervical test results (unless the patient to whom the test belongs objects to its inclusion in the register) to the relevant state or territory population-based cervical cytology register.

Cervical screening programs in each state and territory interrogate their own cervical cytology register in accordance with detailed data specifications to supply unit record level data to the AIHW. These data are compiled into a database.

Institutional environment

The AIHW is a major national agency set up by the Australian Government under the *Australian Institute of Health and Welfare Act* 1987 to provide reliable, regular and relevant information and statistics on Australia's health and welfare. It is an independent statutory authority established in 1987, governed by a management Board, and accountable to the Australian Parliament through the Health and Ageing portfolio.

The AIHW aims to improve the health and wellbeing of Australians through better health and welfare information and statistics. It collects and reports information on a wide range of topics and issues, ranging from health and welfare expenditure, hospitals, disease and injury, and mental health, to ageing, homelessness, disability and child protection.

The Institute also plays a role in developing and maintaining national metadata standards. This work contributes to improving the quality and consistency of national health and welfare statistics. The Institute works closely with governments and non-government organisations to achieve greater adherence to these standards in administrative data collections to promote national consistency and comparability of data and reporting.

One of the main functions of the AIHW is to work with the states and territories to improve the quality of administrative data and, where possible, to compile national data sets based on data from each jurisdiction, to analyse these data sets and disseminate information and statistics.

The *Australian Institute of Health and Welfare Act* 1987, in conjunction with compliance to the *Privacy Act* 1988 (Cwth), ensures that the data collections managed by the AIHW are kept securely and under the strictest conditions with respect to privacy and confidentiality.

For further information see the AIHW website <www.aihw.gov.au>.

The AIHW has been receiving cervical screening safety monitoring data since 2008.

Timeliness

Cervical cytology data are available within about 6 months (there can be a lag of up to 6 months in the transmission of test results from pathology laboratories to cervical cytology registers), and data for the previous calendar year are supplied in July.

The current cervical screening safety monitoring data contains all low-grade cytology and high-grade histology tests performed and reported to the cervical cytology registers from 1 January 2007 to 31 December 2012.

Accessibility

Cervical screening safety monitoring data appear for the first time in *Report on the activity of the National Cervical Screening Program,* and are thereafter published annually in the report *Cervical screening in Australia*, as of the 2011–2012 report, available on the AIHW website <http://www.aihw.gov.au/cervical-cancer-screening/> where they can be downloaded without charge.

General enquiries about AIHW publications can be made to the Media and Strategic Engagement Unit on (02) 6244 1032 or via email to <info@aihw.gov.au>.

Interpretability

While many concepts are easy to interpret, other concepts and statistical calculations are more complex and may be confusing to some users. All concepts are explained within the body of the report presenting these data, along with footnotes to provide further details.

Relevance

Cervical screening safety monitoring data are highly relevant for monitoring the safety of the NHMRC Guidelines. The data are used for many purposes by policy-makers and researchers, but are supplied and analysed specifically to monitor and inform the SMC in this forum.

Accuracy

All data provided by state and territory cervical screening programs, once analysed, are verified to ensure accuracy.

Coherence

Cervical screening safety monitoring data are reported and published annually by the AIHW from 2014.

Appendix D Statistical methods

Data rules

Data on deaths and cervical cancer diagnoses were gained from the state and territory cervical cytology registers.

As date of death data were only available by year, deaths were assumed to occur on 30th June of that year, unless a woman died in the same year as her most recent test. It was then assumed that the date of death was half-way between the date of the most recent test and the end of the year.

Cancer histology and high-grade histology results provided to the AIHW were mapped to their respective categories according to the National Cervical Cancer Prevention Dataset, developed in discussion with the state and territory cervical cytology registers.

Age groups used to check for age-specific differences within cohorts were 20–29, 30–49 and 50–69 for Parameter 1, and 20–39 and 40–69 for Parameter 2.

Methods

Safety monitoring parameters

The method of measuring incidence of cervical cancer within 2 years of an index low-grade cytology test used in this paper was the person-time approach. Follow-up time is calculated from any low-grade cytology test in the reference period, and is stopped (censored) at event of cancer, end of reference period (or 5 years) or death.

Crude rates

A crude rate is defined as the number of events over a specified period of time (for example, a year) divided by the total population. For example, a crude cancer incidence rate is defined as the number of new cases of cancer in a specified period of time divided by the population at risk.

Age-standardised rates (AS rates)

Rates are adjusted for age to facilitate comparisons between populations that have different age structures, for example, between youthful and ageing communities. There are two different methods commonly used to adjust for age. In this publication, we use direct standardisation in which age-specific rates are multiplied against a constant population (the 2001 Australian Standard Population unless otherwise specified). This effectively removes the influence of age structure on the summary rate, described as the age-standardised rate.

The method used for this calculation comprises three steps:

- Calculate the age-specific rate (as shown above) for each age group.
- Calculate the expected number of cases in each 5-year age group by multiplying the age-specific rates by the corresponding standard population and dividing by the appropriate factor (for example, per 100,000 women).

- To give the age-standardised rate, sum the expected number of cases in each group, divide by the total of the standard population and multiply by the appropriate factor (for example, per 100,000 women).

Confidence intervals

Population numbers for incidence and screening have a natural level of variability for a single year above and below what might be expected in the mean over many years. The percentage variability is small for large population numbers but high for small numbers such as incidence in a young age group. One measure of the likely difference is the standard error, which indicates the extent to which a population number might have varied by chance in only 1 year of data.

The 95% confidence intervals presented in this paper were calculated using a method developed by Dobson et al. (1991) and assumed that incidence and screening counts were Poisson random variables. For an observed count, based on data from a single year, there are 19 chances in 20 that the associated confidence interval contains the corresponding annual average (for several years).

Kaplan-Meier estimates (cumulative incidence curves)

Kaplan-Meier methods are standard methods used to estimate the frequency distribution (or incidence curve) of an event over time. In this paper, the method estimates the probability of cervical cancer for each week from the date of an abnormality finding. The Kaplan-Meier estimate is a function of both the weekly and cumulative incidence rates.

Separate incidence curves are calculated for the baseline and ongoing cohorts and the log-rank statistic is used to determine whether the two distributions are significantly different. This shows whether or not there is a statistically significant difference in the rate of progression to cancer (following an abnormality) associated with the change in guidelines.

Proportional hazard regression rates

Proportional hazards regression allows the analysis of the effect of several risk factors on survival, or in this case, cervical cancer diagnosis. Proportional hazard regression modelling was used to estimate the ratio of the likelihood of cancer diagnosis for the ongoing cohort to that for the baseline cohort. Specifically, time to diagnosis was modelled as a function of a random variable indicating the cohort to which an individual belongs; value zero was assigned to the baseline cohort and value one to the ongoing cohort. The estimated regression coefficient was interpreted as this ratio in the chance of diagnosis. This interpretation relies on the 'proportional hazards' assumption that the probability of diagnosis within the ongoing cohort, relative to that in the baseline cohort, is constant over time.

Mantel-Haenszel rate ratios

Mantel-Haenszel methods allow for the stratified analysis of the relationship between two groups, after controlling for various confounding factors. This method is generally valid for small-moderate samples sizes; however, zero values within individual strata may affect validity.

Sequential monitoring

We perform a two-sided test of the hypothesis that the hazard ratio (of the ongoing to the baseline cohort) is equal to one, or equivalently, that the logarithm of the hazard ratio is zero.

The test statistic is calculated with the following formula:

$$\frac{\log[hazard\ ratio]}{SE[\log[hazard\ ratio]]}.$$

In a non-sequential experiment we would reject the null hypothesis (that there is no difference) if the value of this statistic exceeds 1.96 (critical value at the 5% α-level). However, in analysis of the sequential Safety Monitoring data the critical value of 1.96 is replaced by the Wang and Tsiatis (1987) values for eight monitoring points.

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This report looks at the evidence collected and assessed by the Safety Monitoring Committee established to assess whether there were adverse outcomes following the introduction of new NHMRC guidelines on how women with a low-grade Pap test result or a treated high-grade cervical biopsy result should be managed.

Acknowledging that new evidence may come to light in future which could affect this picture, the overarching message from the evidence currently available and the methods used to assess this evidence is that the new guidelines have not led to an increase in cervical cancer in the seven years since they were introduced.