Declining endocervical rates: does it matter?

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Victorian Cervical Cytology Registry
Outline

• Background
• Current recommendations – Australian and international
• Review key studies
• Data from AIHW and VCCR
• Analysis of VCCR-ongoing
Background

• The aim of a Pap test is to sample the transformation zone of the cervix
• Presence of endocervical cells indicates the TZ has been sampled
• A cervical cytology test with no endocervical component (no endocervical cells present E0 or E-) has only squamous cells for evaluation of presence of abnormalities
Figure 2.5 The transformation zone of the cervix of a parous woman of reproductive age

Figure 2.6 The process of squamous metaplasia

a. From birth to prepuberty:
The original squamocolumnar junction is present in girls at birth, and is found at or near the external os.

b. From menarche to early reproductive age:
At puberty, when the ovaries begin to secrete estrogen, the cervix grows in size, columnar cells from the endocervix and the original SCJ become visible on the outer cervix.

c. In women in their 30s:
Under the influence of estrogen, the normal maturing process, known as squamous metaplasia, takes place, and both original and new SCJs are visible.

d. In perimenopausal women:
As women age and the influence of estrogen decreases around menopause, the cervix shrinks, and the columnar epithelium and transformation zone retreat back from the outer cervix into the endocervical canal.

e. In postmenopausal women:
Without estrogen stimulation, the original SCJ is still visible on speculum examination, but the new SCJ and a variable portion of the metaplastic epithelium of the transformation zone have retreated into the cervical canal.

Background

• Clinical importance
Women with repeated smears without endocervical component

• Policy relevance
Declining endocervical rates observed over last 10 years, is this cause for concern?
Reasons for absent endocervical component

Multifactorial

• Sampling technique and instruments
• Laboratory reporting
• Postmenopausal women
• Oral contraceptive use
• Pregnancy
• HRT
• Prior treatment for abnormalities
Background

• Presence of an endocervical component was traditionally considered an indicator of specimen adequacy
• In the past there was limited clinical consensus about significance of E- smears
• Australian 1994 guidelines:
  • repeat negative tests at 2 years irrespective of endocervical component
  • Sheet of 6 endocervical columnar cells or 10 single cells minimum criteria
  • Suggested minimum of 75% smears should have EC
Australian recommendations

• Australian coding terminology does not require endocervical component for a satisfactory smear
• There is no clear recommendation for proportion of smears that should have endocervical component
• “presence of endocervical component in 80% of Pap tests generally considered acceptable”

*Cancer Council Australia 2007*
Australian recommendations

• NHMRC guidelines 2006
  – Cytology reports should include statement regarding presence or absence of endocervical component
  – Should include at least 2 groups of well-preserved endocervical and/or squamous metaplastic cells, each group containing at least 5 cells
  – Lack of endocervical component does not influence screening recommendation
  – No recommended minimum proportion of smears with EC
International recommendations

• Studies conducted since 2000 contribute to evidence suggesting women with smears lacking endocervical component are not at increased risk of high-grade disease

• Bethesda system was revised and endocervical component is no longer required for a satisfactory smear

• Dutch no longer require repeat smear at 6 mths for E-

• Canada – Most guidelines silent on the issue of E-
Why is this an issue now?

• Concern regarding declining rates of smears with an endocervical component over last 10 years in Australia
• Is therefore Pap smear quality declining?
• Are there any adverse outcomes for women because of this decline?
% smears lacking endocervical component by age, AIHW

No endocervical component by age

Source: AIHW analysis of state and territory cervical cytology register data; data for figure are available in Table A1.

Figure 3.2: Proportion of cytology tests with no endocervical component by age, 2009
Increase in Pap smears without endocervical component, Australia 2004-2009

Table 3.8: Cytology tests with no endocervical component, women aged 20–69 years, 2004 to 2009

<table>
<thead>
<tr>
<th></th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>350,670</td>
<td>379,531</td>
<td>387,918</td>
<td>406,736</td>
<td>407,942</td>
<td>418,527</td>
</tr>
<tr>
<td>Crude rate</td>
<td>17.4</td>
<td>18.5</td>
<td>19.1</td>
<td>19.4</td>
<td>19.8</td>
<td>20.1</td>
</tr>
<tr>
<td>AS rate</td>
<td>17.9</td>
<td>19.0</td>
<td>19.5</td>
<td>19.8</td>
<td>20.2</td>
<td>20.3</td>
</tr>
<tr>
<td>95% CI</td>
<td>17.8–17.9</td>
<td>18.9–19.0</td>
<td>19.5–19.6</td>
<td>19.8–19.9</td>
<td>20.1–20.2</td>
<td>20.3–20.4</td>
</tr>
</tbody>
</table>

Note: Crude rate is the number of cytology tests with no endocervical component as a proportion of the total number of cytology tests; Age-standardised (AS) rate is the number of cytology tests with no endocervical component as a proportion of the total number of cytology tests age-standardised to the Australian population at 30 June 2001.

Source: AIHW analysis of state and territory cervical cytology register data.
Endocervical component VCRR, 2001-2010

- Crude rate
- AS rate

Year
2001 2002 2003 2004 2005 2006 2007 2008 2009 2010
Percentage
0 5 10 15 20 25 30

Victorian Cervical Cytology Registry
% E- by age and year, VCCCR
Figure 7.1 Proportion of Victorian Pap tests collected by nurses and other providers, types with an endocervical component

![Graph showing the proportion of Victorian Pap tests collected by nurses and other providers, types with an endocervical component. The graph illustrates a decline in the percentage of tests over the years 2001 to 2010, with a comparison between nurses and other practitioners.]
Does it matter?

• Early repeat testing for women with E0 smears would be justified if it were shown that significant additional disease was detected on later smears (ie disease was missed in the initial E0 smear )

• The weight of the evidence has suggested this is not the case
Study design

• Importance of cross-sectional vs longitudinal design in addressing this question

• Cross-sectional design, with no follow-up cannot address the question of prognostic relevance of endocervical status in negative smears
Smear 1

- E-
  - Rate of high grade disease

Smear 2

- E-
  - Rate of high grade disease

- E+
  - Rate of high grade disease

or no difference
Previous studies - VCS


Mitchell HS. Longitudinal analysis of histologic high-grade disease after negative cervical cytology according to endocervical status. Cancer 2001;93:237-40


Mitchell H, Medley G. cytological reporting of cervical abnormalities according to endocervical status. Br J Cancer 1993;67:585-8
Previous studies

Mitchell and Medley  *Br J Cancer* 1993

- Improved provision of sampling instruments and educational materials at Victorian Cytology Service
- Reported increase in reporting of endocervical component 1987-91 from 50% -80%
- No increase in rate of high grade disease over that period of time, non-significant increase in adenocarcinoma
- Lower rate of high-grade disease among women without endocervical component
Previous studies

- Heather Mitchell *Cancer Cytopath* 2001
- Longitudinal analysis of VCCR data

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Smear 1</th>
<th>Smear 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>E+</td>
<td>E+</td>
</tr>
<tr>
<td>B</td>
<td>E-</td>
<td>E+</td>
</tr>
<tr>
<td>C</td>
<td>E+</td>
<td>E-</td>
</tr>
<tr>
<td>D</td>
<td>E-</td>
<td>E-</td>
</tr>
</tbody>
</table>
## Incidence of High grade disease in E+ and E- cohorts

Table 2. Standardized Incidence Ratios for Histologic High-Grade Disease

<table>
<thead>
<tr>
<th></th>
<th>Cohort A</th>
<th>Cohort B</th>
<th>Cohort C</th>
<th>Cohort D</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of women with high-grade histology within 6 mos of subsequent smear</td>
<td>89</td>
<td>62</td>
<td>18</td>
<td>7</td>
</tr>
<tr>
<td>Crude incidence rate of histologic high-grade disease per 1000 yrs of follow-up</td>
<td>2.92</td>
<td>2.59</td>
<td>0.67</td>
<td>0.55</td>
</tr>
<tr>
<td>Standardized incidence ratio (95% CI)</td>
<td>1.00</td>
<td>0.89 (0.67–1.12)</td>
<td>0.24 (0.13–0.36)</td>
<td>0.26 (0.07–0.45)</td>
</tr>
<tr>
<td>P value</td>
<td>&gt; 0.05</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
</tbody>
</table>

95% CI: 95% confidence interval.

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Mitchell HS *Cancer Cytopathology* 2000:93(4)
Incidence of low grade disease in E+ and E- cohorts

Table 3. Standardized Incidence Ratios for Histologic Low-Grade Disease

<table>
<thead>
<tr>
<th></th>
<th>Cohort A</th>
<th>Cohort B</th>
<th>Cohort C</th>
<th>Cohort D</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of women with low-grade histology within 6 mos of subsequent smear</td>
<td>106</td>
<td>54</td>
<td>28</td>
<td>10</td>
</tr>
<tr>
<td>Crude incidence rate of histologic low-grade disease per 1000 yrs of follow-up</td>
<td>3.48</td>
<td>2.25</td>
<td>1.04</td>
<td>0.79</td>
</tr>
<tr>
<td>Standardized incidence ratio (95% CI)</td>
<td>1.00</td>
<td>0.67 (0.49-0.85)</td>
<td>0.32 (0.20-0.44)</td>
<td>0.32 (0.12-0.51)</td>
</tr>
<tr>
<td>P value</td>
<td>&lt; 0.01</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
</tbody>
</table>

95% CI: 95% confidence interval.

Mitchell HS Cancer Cytopathology 2000:93(4)
Previous studies

Rossi et al  *ACTA Cytologica 2010*

- Prospective Italian study of 11 screening programs
- Women with negative smears were classified as E+ or E- at entry  NB E- rate 4%
- Endpoint CIN2+ histology
- 4.5 years followup, restricted to 25-50 yo
- CIN2+ rate was 2.06 per 1000 for E+ and 1.09 per 1000 for E-
- RR = 0.55 95% CI (0.28-1.06)
Previous studies

• Rossi et al *ACTA Cytologica* 2010
• In general E- smears may reflect lower quality smears
• Lower risk of CIN2+ among women with E-smears therefore no need for early repeat smear (3 years in Italy)
• May be useful as operator specific indicator of sampling performance
Previous studies

• Siebers et al *Cytopathology 2003* Dutch study 24 mths follow up
  – Lower rates of HSIL+ cytology in subsequent E-smears

• Bos et al *Am J Clin Pathol 2001* Longitudinal study with cancer as endpoint
  – 0.54 per 1000 for E+ vs 0.53 per 1000 for E-
2011 Review

*Elumir-Tanner et al CMAJ 2011*

- The majority of recent studies do not support early retesting for women whose smears lack endocervical component, no increase in high-grade disease
- Gaps: longer followup (reduce verification bias), biological mechanisms for difference in rates of disease, cancer outcomes
Does it matter?

- Early repeat testing for women with E0 smears would be justified if it were shown that significant additional disease was detected on later smears (ie disease was missed in the initial smear without endocervical component)
Detection of high-grade histologically confirmed abnormalities over time, AIHW
Detection of high-grade histologically confirmed abnormalities over time, AIHW

  • In 2004 7.7 per 1000 women screened 95%CI (7.6-7.9)
  • In 2009 8.1 per 1000 women screened 95%CI (8.0-8.2)
Detection of endocervical abnormalities (cytology) 2004-2009, AIHW
Figure 6.4: Incidence of carcinoma of the cervix (squamous cell carcinoma, adenocarcinoma, adenosquamous carcinoma and other carcinoma), women aged 20–69 years, by year, 1982 to 2007

Note: The rates were age-standardised to the Australian population as at 30 June 2001.
Source: AIHW Australian Cancer Database.
Figure 8.2: Age-standardised incidence rates (ASR) for cervical cancer by histological subtype in Victoria, 1982–2008.

Other cancers are comprised of cervical adenocarcinomas, mixed adenosquamous carcinomas, small cell carcinomas and carcinosarcomas/sarcomas.

ASR is the age-standardised incidence rate.

Further analyses

• VCCR database 5.9 million episodes
• Retrospective cohort of 1.7 million women screened 2000-2010
• Enter with negative smear, categorised based on E-/E+
• Up to 10 years of followup
• Analysis in progress, completion by end of year.
Summary

• The reasons for changing E-rates in Australia since 2000 are probably multifactorial and there is variation by state

• Smear taking techniques, laboratory reporting, and other factors such as prevalence of treatment, age at first birth, and OC use may all play a role

• Monitoring of E-smears by practitioner is useful at the individual level
Summary

• Since 2000, high-grade abnormalities have remained relatively constant over time across all ages (>20 years), slight increase 2008-09
• Indeed cancer rates have continued to decline
• No change in rate of endocervical abnormalities or adenocarcinoma over time
• Evidence from longitudinal VCCCR analysis will be available shortly
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