Screening for cervical disease

Putting invasive cervical cancer in perspective

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Topics

1. Screening to prevent invasive cancer
2. False negative screening tests in women with invasive cancer
3. Screening test trials and verification bias
4. Selective co-testing for women at increased risk
Screening is effective at reducing invasive cancer rates

Cervical Cancer registrations and mortality in New Zealand, 1990-2011

How does cervical screening work?

• detects treatable pre-invasive lesions to prevent invasive cancer developing
  – reduces incidence and therefore mortality rates

• detects cancer that is already invasive
  – benefit is detection at an earlier stage of disease which reduces morbidity and mortality rates
High-grade pre-invasive and invasive histology reports NZ 2013

Number of histology reports

- HG Pre-invasive lesions
- Invasive cancer

Source: NCSP Annual report 2013

1: Screening is effective mainly because the ability to detect treatable high-grade pre-invasive cervical lesions allows us to prevent invasive cervical cancer

- CIN2/3+ is a highly suitable endpoint for studies about screening effectiveness because CIN2/3 is primarily what we are trying to detect

- CIN2/3 is not being used as a surrogate marker for invasive cancer: it is exactly the lesion we want to find
The ARTISTIC Trial (UK): A Randomised Trial In Screening to Improve Cytology

To address the following questions:

1. Does the combination of cytology and HPV testing achieve a reduction in CIN 3+?
2. Is HPV testing cost-effective in primary cervical screening?
3. Is its use associated with psychosocial or psychosexual effects?
4. How would it perform as an initial screening test followed by cytology for HPV positivity?

Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials

• Combined data: HPV-based screening provides 60-70% protection from invasive cervical carcinoma compared with cytology
What about women with invasive cancer?

• we don’t know (yet) why some women with persistent high-grade cervical lesions go on to develop invasion while others don’t so we don’t know how to test for this difference
• screening tests can identify pre-symptomatic women with invasive cancer or identify those at higher risk
• False negative results that miss invasion are a serious concern

Invasive cervical cancer cases

<table>
<thead>
<tr>
<th>Has invasive cervical cancer</th>
<th>Screening test positive</th>
<th>Screening test negative</th>
<th>Totals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Has invasive cervical cancer</td>
<td>6</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Doesn’t have invasive cancer</td>
<td>1</td>
<td>99,992</td>
<td>99,993</td>
</tr>
<tr>
<td>Totals</td>
<td>7</td>
<td>99,993</td>
<td>100,000</td>
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Screening test sensitivity = 6/7 (86%)
False negative rate among women with invasive cancer
= 1/7 (14%)
HPV test false-negative rates with cervical cancer diagnoses

HC-2 HPV tests on cervical cytology samples were negative in patients with cervical cancer in 6.6-12.6% of cases in 5 international studies
  – false negative rate among a total of 1072 invasive cases across all 5 studies was 10%
  – Sensitivity for HC-2 detection of ICC = 90%

Dr Marshall Austin: talk to Cartwright Collective
   (Auck 2016)

False negative rate of LBCytology for invasive cervical cancer detection

Retrospective review of all cytology for all invasive cancer cases diagnosed in 2008-9 at two major Danish screening centers
11/112 = 9.8% were diagnosed with false negative cytology
*Kirschner et al Gynecol Oncol 2011 Jan;120(1):68-72*

Invasive cancer cases (n= 1490) diagnosed on or after 1 July 2012: LBC slides reported < 10 years of invasion
115 negative results from 1891 cytology tests = 6.1%
*NHSCSP Audit of invasive cervical cancer: National Report 2009-2013*
### Invasive cervical cancer cases

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- If you improve the detection of preinvasive lesions, the number of invasive cancers will fall.
- The false negative rate within the population of women with invasive cancer could rise \((1/5 = 20\%)\), even though there are fewer cases of invasive cancer in the population.

2: The false negative rate of a screening test for women with invasive cervical cancer can be affected by the ability of the screening test to reduce invasive cancer rates in the population.

- A higher false negative rate could occur with the same number of cases that are missed by screening, if the total number of cases of women with invasive cancer has reduced.
Comparison of cervical cancer screening results among 256,648 women in multiple clinical practices *Cancer Cytopathology* May 2015 Blatt et al

- 256,648 women 30-65 years with a cervical biopsy and a previous cotest *within one year before the biopsy*.
- Cyto = LBC (TP & SP), HPV test = HC-2
- Results: 526 = total cancers
  - HPV neg: 98/526 = 18.6%
  - Cyto neg: 64/526 = 12.2%
  - Co-test neg: 29/526 = 5.5%
- Conclusion: Co-testing was best way to identify women with invasive cervical cancer

Prior hrHPV testing and Pap test results of 70 invasive cervical carcinomas diagnosed in 2012 *Arch Pathol Lab Med* Feb 2015;139: 184-188 Zhao et al

- multicentre study (18 laboratories)
- review of prior hrHPV testing (HC-2, Cervista, Cobas) and Pap test results (LBC = TP or SP) for *5 years prior to cancer diagnosis*.
- Results:

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<th>Cyto neg</th>
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<tbody>
<tr>
<td>3-5 years</td>
<td>40%</td>
<td>20%</td>
</tr>
<tr>
<td>1-3 years</td>
<td>20%</td>
<td>10%</td>
</tr>
<tr>
<td>&lt; 1 year</td>
<td>10%</td>
<td>5%</td>
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- Conclusion: “data expose limitations for the potential use of primary HPV testing”
Verification bias

A population of women with/without a HG lesion

= no high grade cervical lesion

= has a high grade cervical lesion

Acknowledgement for model: Dr Thomas Wright

Screened with cytology

= no high grade cervical lesion

= has a high grade cervical lesion

Cytology HG+ve
Women with a HG lesion identified by colposcopy and biopsy

= no high grade cervical lesion  = has a high grade cervical lesion

Cytology HG+ve

HG +ve by colp with bx

Look-back study of Biopsy +ve (HG) women

Cytology HG+ve

HG +ve by colp with bx

Verification bias will overestimate the performance of the test
How does this apply to studies investigating the value of screening tests?

- Verification bias is present in most studies
- Some studies e.g. The Athena trial (USA) specifically control for verification bias
- Cytology and HPV testing detect different stages in the evolution of high-grade lesions so the biases are likely to be different.

How can we limit this effect?

- Look-back studies are particularly difficult because the potential for bias is large
- Colposcope everyone in the study: can’t do this for a large screening population
- Studies over a longer time frame are likely to be better because women with lesions are more likely to be identified.
- Prospective trials limit the effect because there is less case selection bias.
Cervical cancer risk for 330,000 women undergoing concurrent HPV testing and cervical cytology in routine clinical practice at a large managed care organisation *Lancet Oncology* 2011;12(7):663-72 Katki et al

- Prospective study analysing the cumulative CIN3+ and invasive cancer rates for 331,818 women aged 30+ who were cotested and followed for 5 years.

**Findings for invasive cancer**

- 5-year cumulative incidence was extremely low for 315,061 HPV-ve women: 3.8/100,000
- only slightly higher than for 306,969 co-test -ve women: 3.2/100,000
- and half that of the rate for 319,177 cyto –ve women: 7.5/100,000

- HPV+ve cyto –ve women had 29% of the cancers and 63% of the adenocarcinomas
Women with invasive cancer: ARTISTIC TRIAL Rounds 1 and 2

There were 12 invasive cancers in the CIN3+ group

- **Round 1 = 9 cases**
  - 8 detected with CIN2+ cytology and all were HPV +ve
  - 1 (adenocarcinoma) had “borderline” cytology and was HPV -ve

- **Round 2 = 3 cases**
  - One had -ve cytology and was HPV +ve in both rounds
  - One (adenocarcinoma) had -ve cytology in both rounds, was HPV -ve in round 1 and HPV +ve in Round 2
  - One had borderline cytology in both rounds, was HPV -ve in round one and didn’t have a round 2 HPV result

HPV testing and cytology for women with invasive cancer

- both cytology and HPV testing will miss some women with invasive cancer
- using both cytology and HPV testing as a co-test would maximise early detection of invasion
- co-testing doesn't make sense as a screening test for the entire screening population but if there is a reason to suspect that a women is at higher risk of cervical cancer, then we should use co-testing
4: Co-testing women who are at higher risk of having invasive cancer makes sense

Selective co-testing will be used for women who:
- have symptoms suspicious of invasive cancer
- have a positive hrHPV screening test (any HPV subtype)
- have been treated for a high-grade lesion (test of cure)
- are at greater clinical risk (e.g. immunosuppressed)
  • this is investigation of increased individual risk, not population-based screening of asymptomatic women

Summary

1. Screening is effective mainly because it detects treatable high-grade pre-invasive cervical lesions so that invasive cervical cancer can be prevented

2. The false negative rate of different screening tests for women with invasive cervical cancer can be affected by changes in invasive cancer prevalence attributable to the screening test

3. Prospective trials provide more robust information than retrospective studies because they are less affected by verification biases.

4. Selective co-testing of women who are at higher risk of having invasive cancer makes sense