Systematic review of overdiagnosis in cervical cancer screening

Chisato Hamashima
Teikyo University, Tokyo

The author declares no conflict of interest

Incidence of Cervical Cancer

Trends in incidence of cervical cancer in selected countries:
Age-standardized rate per 100,000

(GLOBOSCAN 2012)
Background

- Cervical cancer screening is a common strategy for cancer control worldwide.
- Although its real target is invasive cervical cancer, the incidence has not been high in developed countries, and precancerous lesions have now become the actual target of cervical cancer screening.
- Therefore, cervical intraepithelial neoplasia (CIN) 3 has now been generally identified as the actual target for early detection and treatment, while, in some countries, CIN2 has become the treatment target.

Natural History of Cervical Cancer

Schiffman M et al. JNCI J Natl Cancer Inst 2011;jnci.djq562
Objective

- The definition of overdiagnosis in cervical cancer screening has been unclear.
- Although most cases of CIN have a high possibility of disappearing, CIN3 lesions have been routinely resected when detected by cervical cancer screening.
- To clarify overdiagnosis frequency in cervical cancer screening, a systematic review was performed.

Ranking of Outcomes for Effectiveness of Cervical Cancer Screening
1. Reduction of mortality from cervical cancer, life-years gained
2. Reduction of morbidity due to cervical cancer: incidence of cancer (Ib+), quality-adjusted life-years gained
3. Reduction of incidence of cancer (including micro-invasive cancer)
4. Reduction of incidence of CIN3 or worse disease (CIN3+)
5. Increased detection rate of CIN2 or CIN3+
6. Increased test positivity with increased, similar, or hardy/reduced positive predictive value

(European guidelines for QA in cervical cancer screening, 2006)
Methods

• Medline, Cochrane Central, Embase, and Igaku-Cyuo zasshi (for Japanese articles) were searched before July 2018. The articles were original articles limited to English-language or Japanese-language publications.

• Search terms such as ‘cervical cancer’, ‘cancer screening’, ‘cytology’, ‘Pap smear’, ‘HPV testing’, and ‘overdiagnosis’ were used.

• A modeling approach was also included. Additional references cited in candidate articles were included as needed.

Flowchart of article selection

Main key word ‘RCT’

Ovid (n=1,436)
Medline (Feb 2018)
Cochrane Central Register (Dec 2017)
Embase (Feb 2018, n=213)

Main key word ‘Overdiagnosis’

PubMed (July 2018, n=134)

Abstract review (n=1,279)
Full text review (n=30)
Candidate articles (n=30)

Abstract review (n=134)
Full text review (n=7)
Candidate articles (n=2)

Duplication n=370

Target articles (n=2)
Finnish RCT


Overdiagnosis was estimated based on CIN3 diagnosed at screen and interval cancer.

|          | Expected incidence | Number of interval cancer | CIN3 detection rate | Benefit | Overdiagnosis | Frequency of Overdiagnosis (%)
|----------|--------------------|----------------------------|---------------------|---------|---------------|-------------------------------
|          |                    |                            |                     |         |               |                               
| P0       | 20                 | 2.5                        | 57.1                | 17.5    | 39.6          | 69.4                          
| P1       |                    |                            |                     |         |               |                               
| P3       |                    |                            |                     |         |               |                               
| P0-P1    | 20                 | 1.4                        | 38.8                | 18.6    | 20.2          | 52.1                          
| P3-(P0-P1)|                   |                            |                     |         |               |                               

Definition of Overdiagnosis in Modeling study


Overdiagnosis was estimated based on MISCAN model.

Overdiagnosis

Population perspective
women aged 30-100 years

Individual perspective
women aged 30-60 years
Results of Modeling study

<table>
<thead>
<tr>
<th>Perspective</th>
<th>Population perspective</th>
<th>Individual perspective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis period</td>
<td>Lifetime</td>
<td>Screening age</td>
</tr>
<tr>
<td>No screening</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of diagnosis without screening</td>
<td>1669</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of screen detected</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIN1+</td>
</tr>
<tr>
<td>CIN2+</td>
</tr>
<tr>
<td>CIN3+</td>
</tr>
<tr>
<td>Cervical cancer</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Overdiagnosis rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIN1+</td>
</tr>
<tr>
<td>CIN2+</td>
</tr>
<tr>
<td>CIN3+</td>
</tr>
</tbody>
</table>

Overdiagnosis rate (%) = Excess diagnosis/Screening diagnosis

Estimation of Overdiagnosis

- In the Finnish study, overdiagnosis was estimated based on the results of one-shot screening. On the other hand, the frequency was estimated in screening age period or lifetime in the Dutch modeling study.
- However, the frequencies of cytology were almost the same, at 50% in both studies.
- In the Finnish study, the frequency of HPV testing is higher than cytology.
Cost-effectiveness analysis of cervical cancer screening

• A search for CEA of cervical cancer screening was performed using PubMed before 2017.
• The articles were original articles limited to English-language or Japanese-language publications.
• Search terms such as ‘cervical cancer’, ‘cancer screening’, ‘cytology’, ‘Pap smear’, ‘HPV testing’, and ‘cost-effectiveness’ were used.

Flowchart of CEA article selection

PubMed4_Medline (Dec 2017, n=152)

Abstract review (n=152)

Full text review (n=69)

Candidate articles (n=17)

Target articles (n=4)

Excluded articles (n=52)

CEA comparisons between cytology, HPV testing alone and co-testing
Results

• Cytology was usually the basic comparator for CEA, but the target age group and the screening intervals were different among countries.
• A lifetime Markov-model was used in CEA for cancer screening.
• Theses models were developed based on the natural history from precursor lesion to invasive cancer.

Typical model of cervical cancer screening

(Vijayaraghan, et al. Gynecol Oncol 2010)
CEA and Overdiagnosis

- In the model, all detected precursor lesions were assumed to progress to invasive cancer. However, there is a huge amount of overdiagnosis in precursor lesions, which cannot be ignored.
- On the other hand, all treatment costs were included.
- When precursor lesions are diagnosed, most are treated based on the assumption of equal progression.

Guidelines for management

<table>
<thead>
<tr>
<th>Guidelines</th>
<th>Target lesions</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>EC QA guidelines</td>
<td>CIN2, CIN3</td>
<td>Women with high-grade CIN require treatment; observational follow-up is not an option.</td>
</tr>
<tr>
<td>American Society of Clinical Oncology</td>
<td>CIN2, CIN3</td>
<td>In basic settings, treatment options are cryotherapy or LEEP. In other settings, LEEP or ablation is recommended.</td>
</tr>
<tr>
<td>American Society for Colposcopy and Cervical Pathology</td>
<td>CIN2, CIN3</td>
<td>CIN 2 remains the consensus threshold for treatment in the United States. Women with unambiguous CIN3 have the immediate precursor to invasive cancer and should not be observed, regardless of age or concern about future fertility.</td>
</tr>
<tr>
<td>Japan Society of Gynecologic Oncology</td>
<td>CIN3</td>
<td>Cervical cone resection (LEEP, Cold conization, etc.) is recommended.</td>
</tr>
</tbody>
</table>
## The USPTSF model

<table>
<thead>
<tr>
<th>Method</th>
<th>Target age</th>
<th>Screening interval</th>
<th>CIN2 and CIN3 detected</th>
<th>CIN3+ detected</th>
<th>Overdiagnosis</th>
<th>Cervical cancer cases</th>
<th>Cervical cancer deaths</th>
<th>Lifetime-years</th>
</tr>
</thead>
<tbody>
<tr>
<td>No screening</td>
<td></td>
<td></td>
<td>0</td>
<td>0</td>
<td></td>
<td>18.9</td>
<td>8.34</td>
<td>63921.3</td>
</tr>
<tr>
<td>Cytology</td>
<td>21-65 y</td>
<td>3 y</td>
<td>160</td>
<td>46</td>
<td>24</td>
<td>2.34</td>
<td>0.76</td>
<td>64181.9</td>
</tr>
<tr>
<td>Cytology &amp; Co-testing</td>
<td>Cytology 21-29 y Co-testing &gt; 30y</td>
<td>5 y</td>
<td>201</td>
<td>54</td>
<td>37.5</td>
<td>1.08</td>
<td>0.3</td>
<td>64193.0</td>
</tr>
<tr>
<td>Cytology &amp; HPV testing alone</td>
<td>Cytology 21-29 y HPV alone &gt; 30 y</td>
<td>5 y</td>
<td>198</td>
<td>53</td>
<td>36.8</td>
<td>1.08</td>
<td>0.29</td>
<td>64193.1</td>
</tr>
</tbody>
</table>

(AHRQ, 2018)

## Discussion

- In cervical cancer screening, precursor lesions have been identified as the target of cancer screening, because the screen-detection of invasive cancer is rare, due to the high frequency of detection of precursor lesions.
- These lesions have been resected, and the adoption of this approach has expanded, despite the high possibility of disappearance of these lesions.
- However, since it is difficult to predict which precursor lesions will progress, most of these lesions are treated if diagnosed.
### Estimates of Overdiagnosis for Breast Cancer Screening

<table>
<thead>
<tr>
<th>Denominator</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malmo</td>
<td>11.7%(82/698)</td>
<td>10.5%(82/780)</td>
<td>18.7%(82/483)</td>
<td>29.1%(82/282)</td>
</tr>
<tr>
<td>Canada 1</td>
<td>14.1%(82/581)</td>
<td>12.4%(82/662)</td>
<td>22.7%(82/361)</td>
<td>29.4%(82/279)</td>
</tr>
<tr>
<td>Canada 2</td>
<td>10.7%(67/626)</td>
<td>93.7%(67/693)</td>
<td>16.0%(67/420)</td>
<td>19.8%(67/338)</td>
</tr>
</tbody>
</table>

(Marmot MG, et al. BJC.2013)

### How should we consider overdiagnosis in CEA for cancer screening?

- If overdiagnosis is ignored, it might underestimate cost-effectiveness.
- To avoid the effects of overdiagnosis, final outcomes (cancer death) should be used for CEA of cancer screening. When a surrogate outcome is used, all treatments and examinations are assumed as benefits.
- The lifetime is the preferable time horizon for CEA of cancer screening because the impact of overdiagnosis depends on the follow-up period.
Guidelines for Cervical Cancer Screening

<table>
<thead>
<tr>
<th>Institute/Country</th>
<th>Published year</th>
<th>Recommended strategy</th>
<th>Target age</th>
<th>Screening Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>US Preventive Task Force</td>
<td>2018</td>
<td>Cytology</td>
<td>21-29</td>
<td>3 year</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cytology + HPV testing</td>
<td>30-65</td>
<td>5 year</td>
</tr>
<tr>
<td>American Society of Clinical Oncology</td>
<td>2017</td>
<td>HPV testing</td>
<td>25-65 (Maximal setting)</td>
<td>5 year</td>
</tr>
<tr>
<td>European Code against Cancer</td>
<td>2015</td>
<td>Cytology</td>
<td>25/30-60/65</td>
<td>3-5 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HPV testing</td>
<td>35-60/65</td>
<td>5 years</td>
</tr>
<tr>
<td>Australia</td>
<td>2017</td>
<td>HPV testing</td>
<td>25-74</td>
<td>5 years</td>
</tr>
</tbody>
</table>

Conclusions

- Overdiagnosis of cervical cancer screening has not been investigated until recently, and its frequency was high in recent reports.
- However, overdiagnosis leads to unnecessary examinations and treatments, and the excess costs increases.
- To clarify the real cost-effectiveness of cancer screening, overdiagnosis should always be considered. When the model is developed, the lifetime with final outcome should be used as the time horizon to avoid overdiagnosis.
The members of Systematic Review Group

- Chisato Hamashima (Teikyo University, Chair)
- Teruhiko Terasawa (Fujita Health University)
- Takafumi Katayama (Hyogo Prefecture University)
- Satoyo Hosono (Nagoya City University)
- Keika Hoshi (Kitazato University)
- Seijyu Sasaki (St. Lukas International Hospital)

Thank you for your kind attention

Chisato Hamashima  MD, PhD
chamashi@med.teikyo-u.ac.jp