IP19: OVERDIAGNOSIS AND ITS EXCESS COST FOR CANCER SCREENING

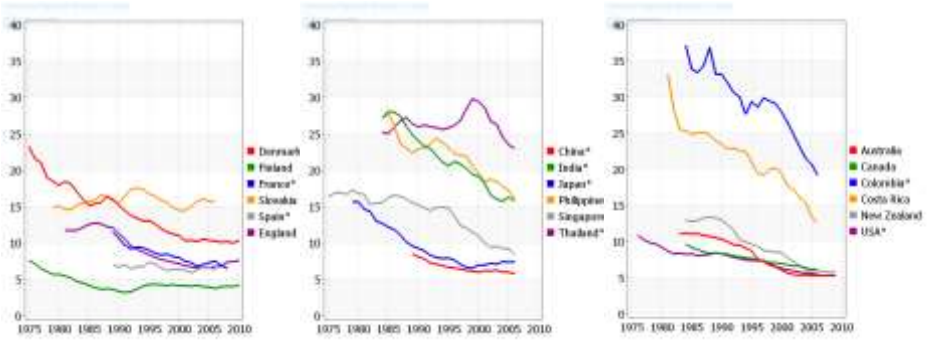
Systematic review of overdiagnosis in cervical cancer screening

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

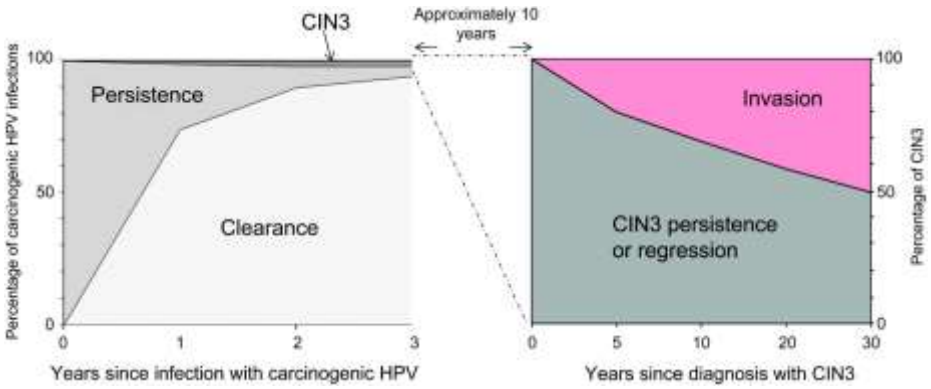


(GLOBOSCAN 2012)

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

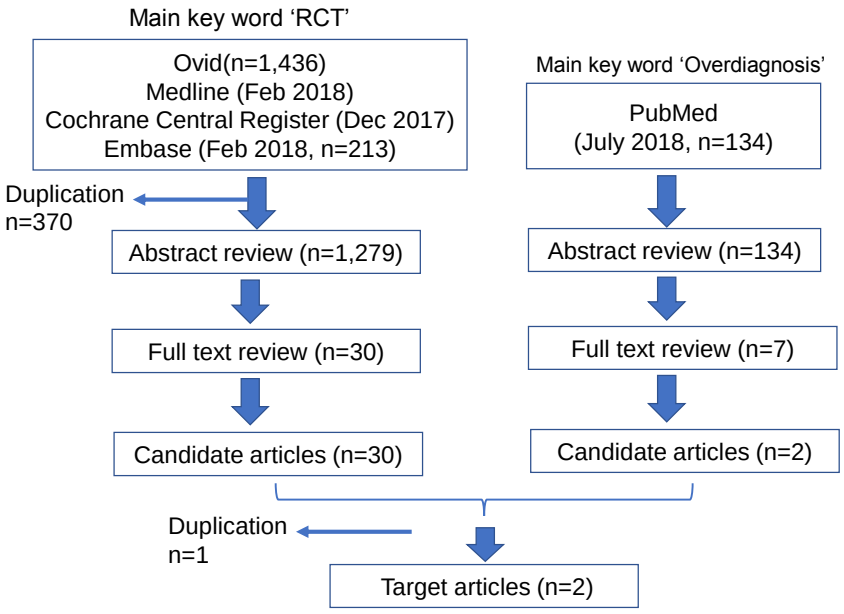
1. Reduction of mortality from cervical cancer, life-years gained
2. Reduction of morbidity due to cervical cancer: incidence of cancer (Ib+), quality-adjusted life-years gained
3. Reduction of incidence of cancer (including micro-invasive cancer)
4. Reduction of incidence of CIN3 or worse disease(CIN3+)
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



Finnish RCT

Malila N, et al. Int J Cancer 132:2141-2147 (2013)

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 (%)
	(/100,000 person-year)					
	P0	P1	P3	P0-P1	P3-(P0-P1)	(P3-(P0-P1))/P3
HPV test	20	2.5	57.1	17.5	39.6	69.4
PAP smear	20	1.4	38.8	18.6	20.2	52.1

Definition of Overdiagnosis in Modeling study

Van Luijt PA, et al. J Mass Screen 23:210-216 (2016)

Overdiagnosis was estimated based on MISCAN model.

Overdiagnosis

Rate
=Number of extra diagnosis with screening/total number of diagnosis with screening

Population perspective

women aged 30-100 years

Individual perspective

women aged 30-60 years

Results of Modeling study

Perspective	Population perspective	Individual perspective
Diagnosis period	Lifetime	Screening age
Number of diagnosis without screening		
No screening	1669	
Number of screen detected		
CIN1+	1138	1138
CIN2+	1189	1189
CIN3+	2593	2593
Cervical cancer	748	424
Overdiagnosis rate (%)		
CIN1+	70.6	74.8
CIN2+	63.2	68.0
CIN3+	50.0	55.4

Overdiagnosis rate (%)= =Excess diagnosis/Screening diagnosis

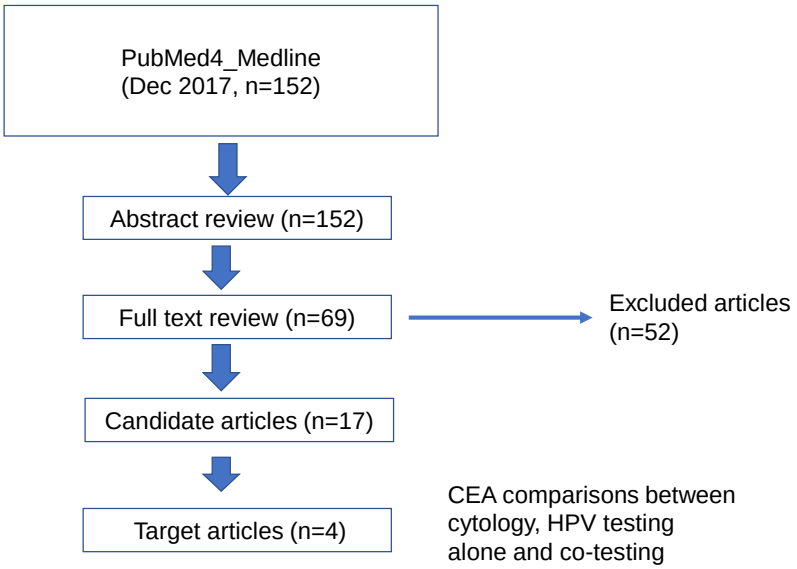
Estimation of Overdiagnosis

- 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 life time 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.

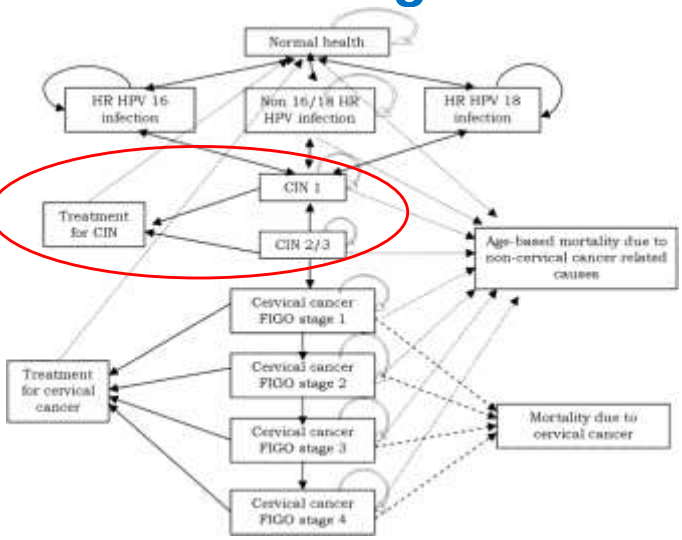
Flowchart of CEA article selection



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

Guidelines	Target lesions	Recommendation
EC QA guidelines	CIN2, CIN3	Women with high-grade CIN require treatment; observational follow-up is not an option.
American Society of Clinical Oncology	CIN2, CIN3	In basic settings, treatment options are cryotherapy or LEEP. In other settings, LEEP or ablation is recommended.
American Society for Colposcopy and Cervical Pathology	CIN2, CIN3	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.
Japan Society of Gynecologic Oncology	CIN3	Cervical cone resection (LEEP. Cold conization, etc.) is recommended.

The USPTSF model

Method	Target age	Screening interval	per 1000 women					
			CIN2 and CIN3 detected	CIN3+ detected	Overdiagnosis	Cervical cancer cases	Cervical cancer deaths	Lifetime-years
No screening			0	0		18.9	8.34	63921.3
Cytology	21-65 y	3 y	160	46	24	2.34	0.76	64181.9
Cytology & Co-testing	Cytology 21-29 y Co-testing > 30y	5 y	201	54	37.5	1.08	0.3	64193.0
Cytology & HPV testing alone	Cytology 21-29 y HPV alone > 30 y	5 y	198	53	36.8	1.08	0.29	64193.1

(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

	A	B	C	D
Denominator	Cancers diagnosis over whole follow-up period in unscreened women	Cancers diagnosis over whole follow-up period in invited women	Cancers diagnosis during screening period in women invited for screening	Cancers diagnosis by screening in women invited for screening
Malmo	11.7%(82/698)	10.5%(82/780)	18.7%(82/483)	29.1%(82/282)
Canada 1	14.1%(82/581)	12.4%(82/662)	22.7%(82/361)	29.4%(82/279)
Canada 2	10.7%(67/626)	93.7%(67/693)	16.0%(67/420)	19.8%(67/338)

(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

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

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