HPV vaccine

Its efficacy & necessity

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Is HPVv effective ！？

Famous article indicating efficiency of Cervarix

Lancet Oncol 2012; 13: 89–99

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rticles

Overall efficacy of HPV-16/18 AS04-adjuvanted vaccine against grade 3 or greater cervical intraepithelial neoplasia: 4-year end-of-study analysis of the randomised, double-blind PATRICIA trial

*Matti Lehtinen, Jorma Paavonen, Cosette M Wheeler, Unnop Jaisamrarn, Suzanne M Garland, Xavier Castellsagué, S Rachel Skinner, Dan Apter, Paulo Naud, Jorge Salmerón, Song-Nan Chow, Henry Kitchener, Júlio C Teixeira, James Hedrick, Genara Limson, Anne Szarewski, Barbara Romanowski, Fred Y Aoki, Tino F Schwarz, Willy A J Poppe, Newton S De Carvalho, Maria Julieta V Germar, Klaus Peters, Adrian Mindel, Philippe De Sutter, F Xavier Bosch, Marie-Pierre David, Dominique Descamps, Frank Struyf, Gary Dubin, for the HPV PATRICIA Study Group**

Reduced number of CIN2+, CIN3+ show the effectiveness to prevent Cervical cancer ?!

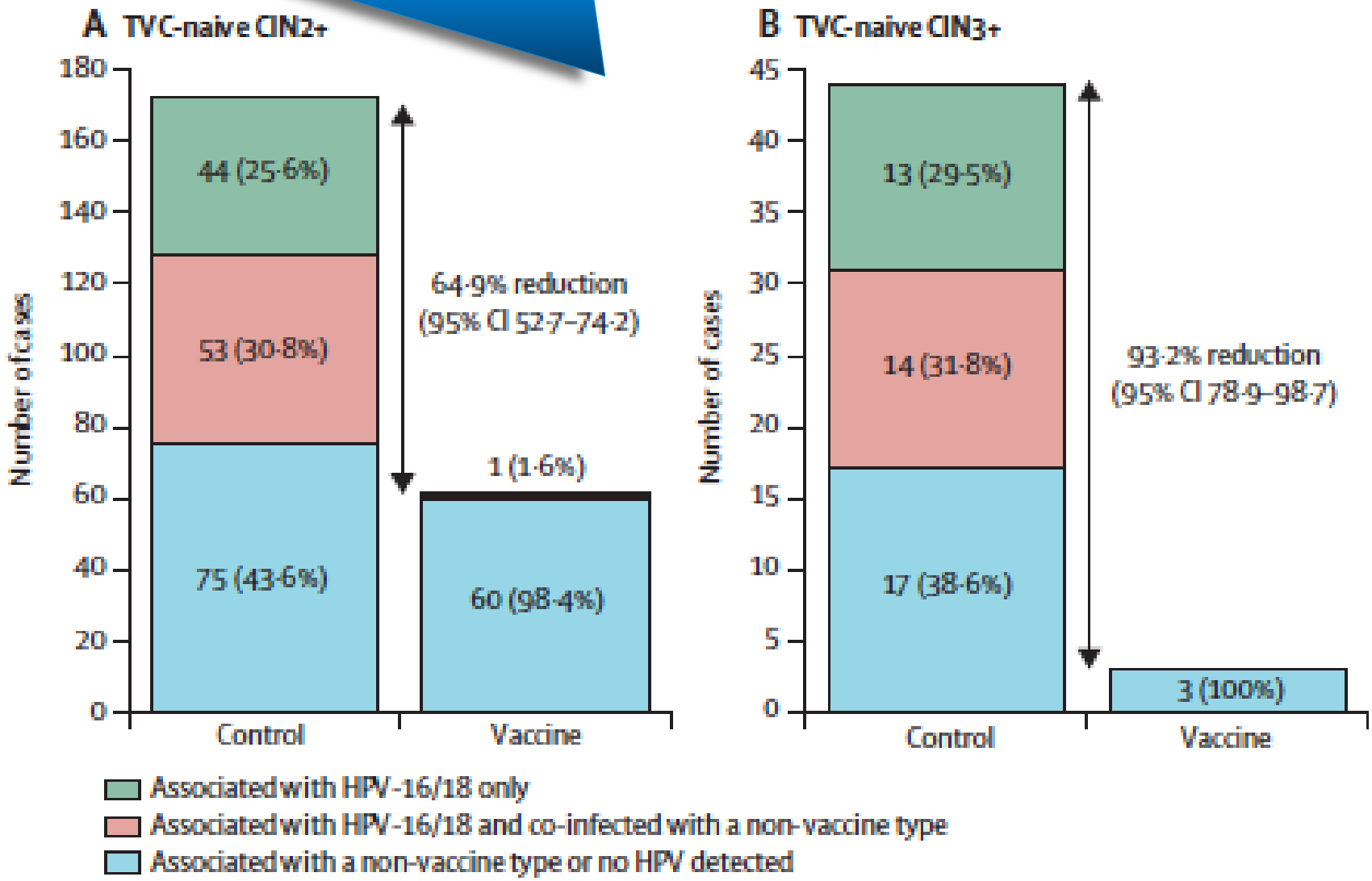
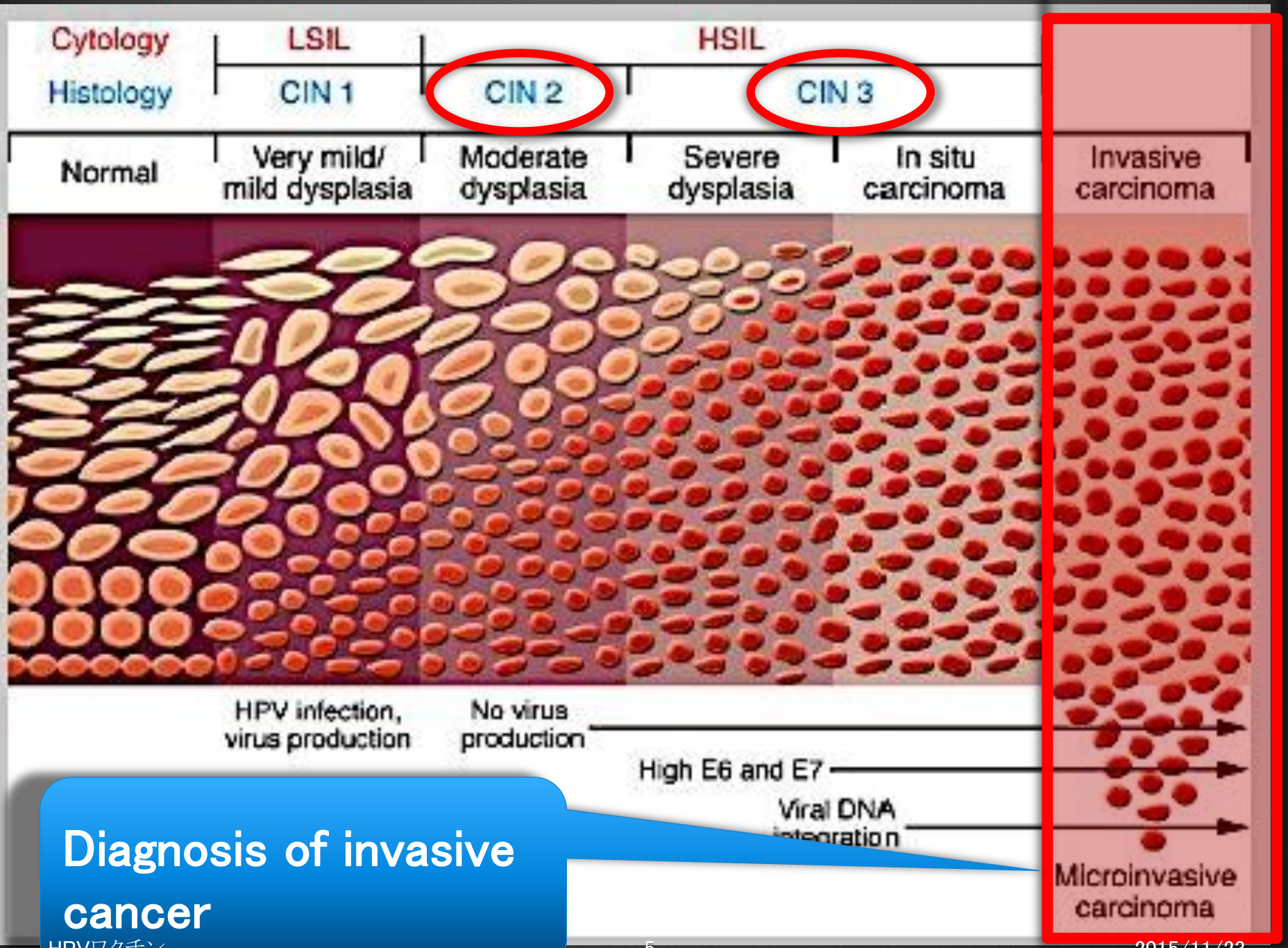


Figure 3: Number of cases of CIN2+ and CIN3+ associated with vaccine and non-vaccine HPV types, in the TVC-naive

CIN 2 +

CIN 3 +



Diagnosis of invasive cancer

J Clin Invest. 2006 May 1; 116(5)

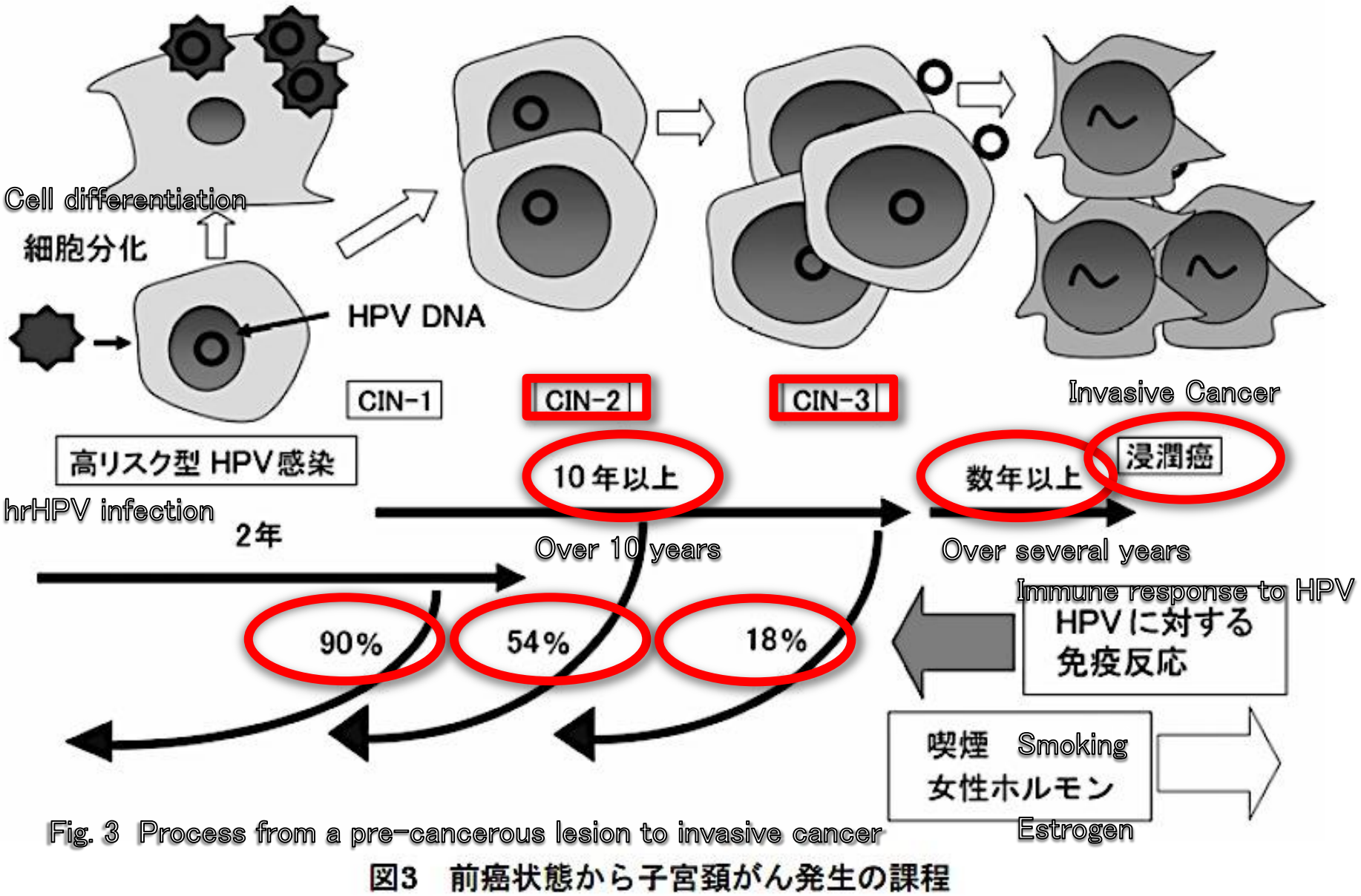


Fig. 3 Process from a pre-cancerous lesion to invasive cancer

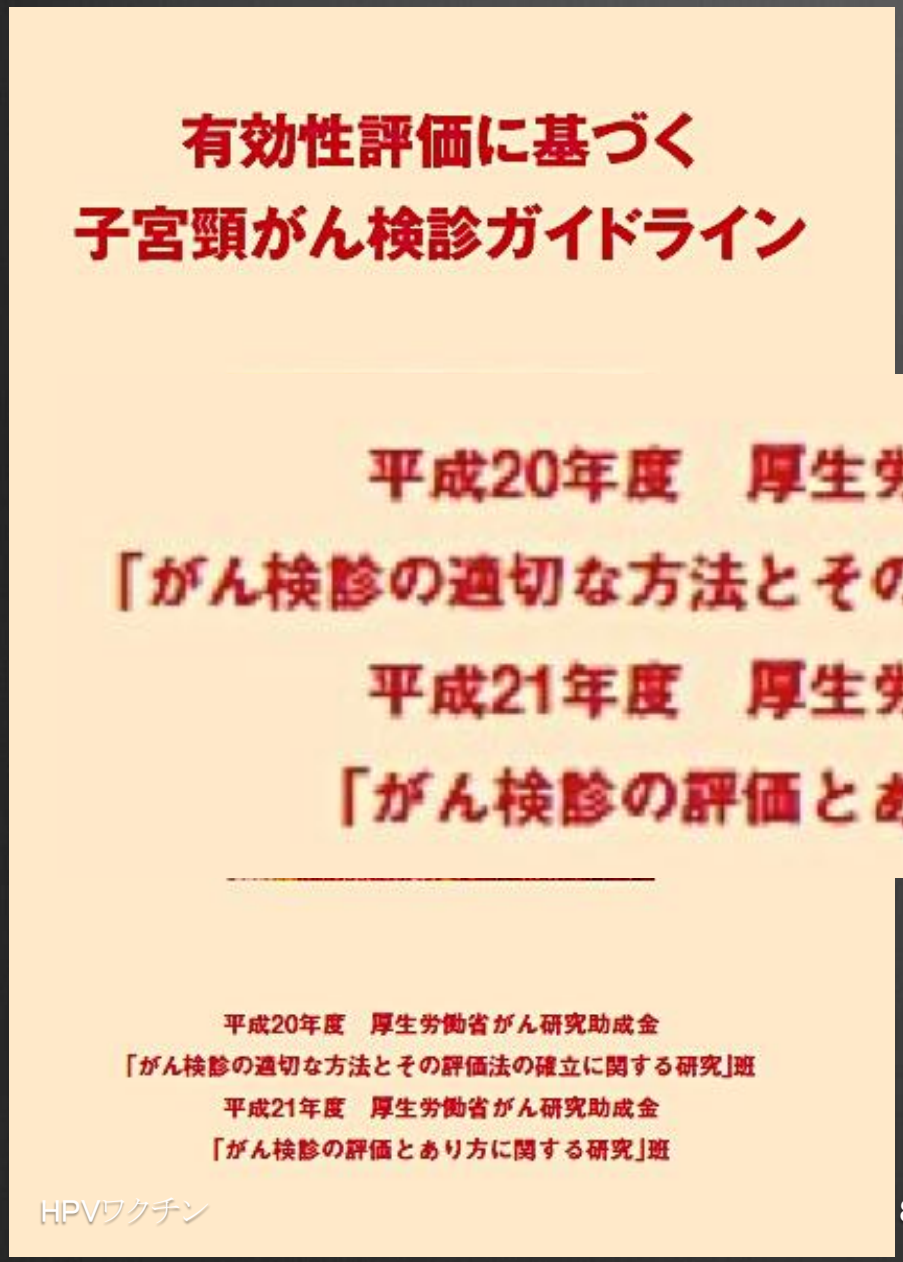
図3 前癌状態から子宮頸がん発生の課程

Lab. Clin. Pract., **24**(1):69-79(2006)

Small part of
CIN 2 +
CIN 3 + progress
to ICC

有効性に関するエンドポイントの設定について

For the setting of the end point on the validity



Guideline of cervical cancer screening based on evaluation of effectiveness

平成20年度　厚生労働省がん研究助成金
「がん検診の適切な方法とその評価法の確立に関する研究」班
平成21年度　厚生労働省がん研究助成金
「がん検診の評価とあり方に関する研究」班

有効性評価に関する子宮頸がん検診特有の問題としては、エンドポイントをどこに定めるかという問題がある。子宮頸がん検診の有効性については子宮頸がん死亡と同様に浸潤がん罹患をエンドポイントとした評価が可能であることが先行研究の成果からすでに確立している。しかし、細胞診従来法について子宮頸がん死亡・浸潤がん罹患と同時に、エンドポイントを CIN3 あるいは CIN2 に拡大し評価した研究はなく、新技術の評価についてもエンドポイントを前がん病変まで拡大することについては慎重に吟味すべきである。子宮頸がんの罹患率や HPV 感染から子宮頸がん発症に至る長い経過を考慮し、IARC ハンドブックでは新技術の短期的な評価には CIN3 以上の病変を[redacted]とした代替指標の利用を容認している。その後に公開された European Commission による精度[redacted]イドラインでも同様の方針をとっている。一方、HPV 検査を用いた子宮頸がん検診に関する無[redacted]較対照試験では、CIN2 以上の病変を代替指標とする評価が行われている。本ガイドライ[redacted]いても、HPV 感染から CIN を経て浸潤がんが発症する自然史がほぼ解明されている子[redacted]については代替指標による評価方法や各種がん検診の評価に応用できるハイリスク[redacted]法を今後の検討課題とする。

To prevent uterine cancer death or invasive cancer incidence, no studies were expanded its endpoint to CIN3, or CIN2. It should be carefully scrutinized to expand the end-point to precancerous lesions.

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「がん検診の評価とあり方に関する研究」班

79p

表5　European Commissionによる精度管理ガイドラインにおける子宮頸がん検診有効性評価のためのアウトカムと研究デザインの信頼性

序列	指標の分類	信頼性	Outcome	アウトカム
1	絶対指標	高い	Reduce mortality from cervical cancer, life-year gaind	子宮頸がん死亡率の減少、生存延長年
2	絶対指標		Reduction of morbidity due to cervical cancer: incidence of cancer (Ⅰb+), quality-adjusted life years gained.	子宮頸がん有病率の減少(Ⅰb以上の子宮頸がんの罹患)、質調整生存年
3	絶対指標		Reduction of incidence of cancer (including micro-invasive cancer)	子宮頸がん罹患の減少(微小浸潤がんを含む)
4	代替指標		Reduction of incidence of CIN3 or worse disease (CIN3+)	CIN3あるいはCIN3以上減少
5	代替指標		Increased detection rate of CIN2+ or CIN3+	CIN2あるいはCIN3の発見率の増加
6	代替指標	低い	Increased test positivity with increased, similar, or hardly reduced positive predictive value	中度が増加するか、同等、あるいは少なくとも減少しな 陽性率が増加する

Detection rate of CIN2+ or 3+ is surrogate endpoint, low reliability on evaluation of the HPVv effect .

How evaluate this paper regarding CIN2+ and 3＋ as surrogate endpoint？ ！

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Articles

Overall efficacy of HPV-16/18 AS04-adjuvanted vaccine against grade 3 or greater cervical intraepithelial neoplasia: 4-year end-of-study analysis of the randomised, double-blind PATRICIA trial

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So “many” COI !

Conflicts of interest

DD, GD, FS, and M-PD are employees of GlaxoSmithKline Biologicals. DD, GD, and FS own stock in GlaxoSmithKline Biologicals, and GD holds a relevant patent. All investigators at study clinical sites were funded through their institutions to do the study protocol. CMW, DA, IP, PN, HK, PDS, FYA, FXB, IH, SRS, SMG, ML, TES, AS, XC, ICT, and BR have received funding through their institutions to do HPV vaccine studies for GlaxoSmithKline Biologicals or Merck Sharp & Dohme (Sanofi Pasteur MSD). IP received a research grant through the Helsinki University Hospital Research Institute to conduct clinical trials on HPV vaccination. SRS has also received funding through her institution from CSL to do research on school-based adolescent HPV vaccination. Through the University of New Mexico, CMW has received equipment and reagents for HPV genotyping from Roche Molecular Systems and funding for HPV vaccine studies from GlaxoSmithKline (in addition to the present study) and Merck & Co. FXB is an editor of the international newsletter (HPV TODAY) and guest editor of the journal *Vaccine* to prepare international reviews on topics related to HPV. WAIP, NSDC, FXB, XC, SMG, PN, BR, TES, and AS have received consulting fees. SMG, SRS, FYA, PN, and TES have received honoraria; TES, BR, and FXB have been paid for expert testimony; BR, FYA, SRS, ICT, NSDC, PDS, and WAIP have received payment for board membership; ICT, FYA, NSDC, XC, PDS, PN, FXB, BR, and TES have received payment for lectures, including service on speakers bureau; AS, FYA, NSDC, PDS, FXB, and BR have received payment for development of educational presentations; and NSDC, IS, WAIP, ICT, SRS, PN, XC, FXB, UL, FYA, IH, SMG, AM, AS, and CMW have received travel reimbursements from GlaxoSmithKline Biologicals or Merck Sharp & Dohme (Sanofi Pasteur MSD), or both. DA has received support for travel from Väestöliitto. S-NC, KP, MJVG, and GL declare that they have no conflicts of interest.

Why HPVv necessary?

To eradicate Cervical cancer Death

Stage	5 y survival of ICC (%)
I	83.2
II	63.0
III	39.2
IV	13.0

Clearly poor prognosis when clinical stage advances

In sites (O stage) : Almost 100% survival if carried out by appropriate treatment

Ia1 (← invasive cancer): 5-y survival rate of 95% or more, pregnancy is also possible.

Evidence Synthesis
Number 86

Screening for Cervical Cancer: A Systematic Evidence Review for the U.S. Preventive Services Task Force

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
540 Gaither Road
Rockville, MD 20850
www.ahrq.gov

Contract No. HHS-290-2007-10057-I, Task Order No. 3

Prepared by:
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Portland, Oregon

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Rongwei Fu, PhD
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AHRQ Publication No. 11-05156-EF-1
May 2011

http://www.ncbi.nlm.nih.gov/books/NBK66099/pdf/Bookshelf_NBK66099.pdf

The rate of progression of CIN3 to cancer has recently been estimated as 31.3 percent in 30 years. This rate was determined using retrospective data from *an unethical clinical study in New Zealand between 1965 and 1974* that left a number of women with CIN3 disease incompletely treated or un

CIN3の 31.3% が30年で浸潤がんになると推測
（ ⇔ translation into Japanese）

Other rough estimates from early studies of precancer suggest a *20 to 30 percent risk of invasion over a 5- to 10-year timeframe.*

CIN3の 20 – 30% が 5 – 10年で浸潤がんの危険
（ ⇔ translation into Japanese）

Studies of women diagnosed with ICC in the 1980s and 1990s in Connecticut and California showed that *50 to 60 percent had not been screened within 3 years of diagnosis.*

浸潤がんと診断された患者の 50 ～ 60% が、この 3年以内にがん検診を受けていない（ ⇔ translation into Japanese）

In the Connecticut study, *about half* of women diagnosed with *ICC had no screening within 5 years*, and about *30 percent had never been screened.*

浸潤がん患者の約半数が、この 5年以内にがん検診を受けておらず、約 30% は一度も受けていない（ ⇔ translation into Japanese）

http://cancerinfo.tri-kobe.org/index.html

Risk factor：

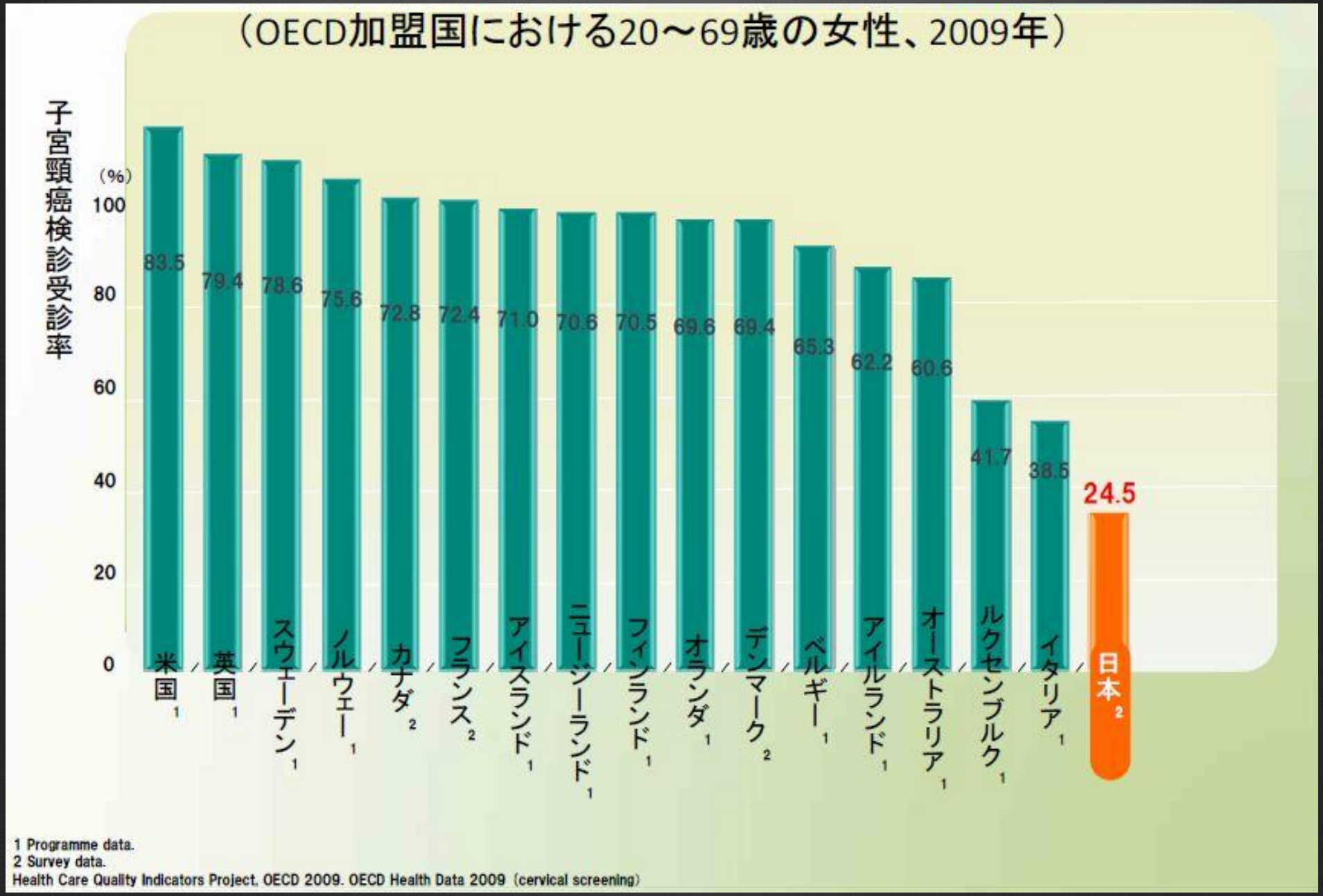
1）HPV infection 2）Immunosuppression 3）Multiple pregnancy 4）Prolonged use of cntraceptives 5）sSmoking etc

Countermeasure：1）Sexual abstinence　2）HPVv inrioculation 3）Use of condom

To eradicate Cervical cancer death

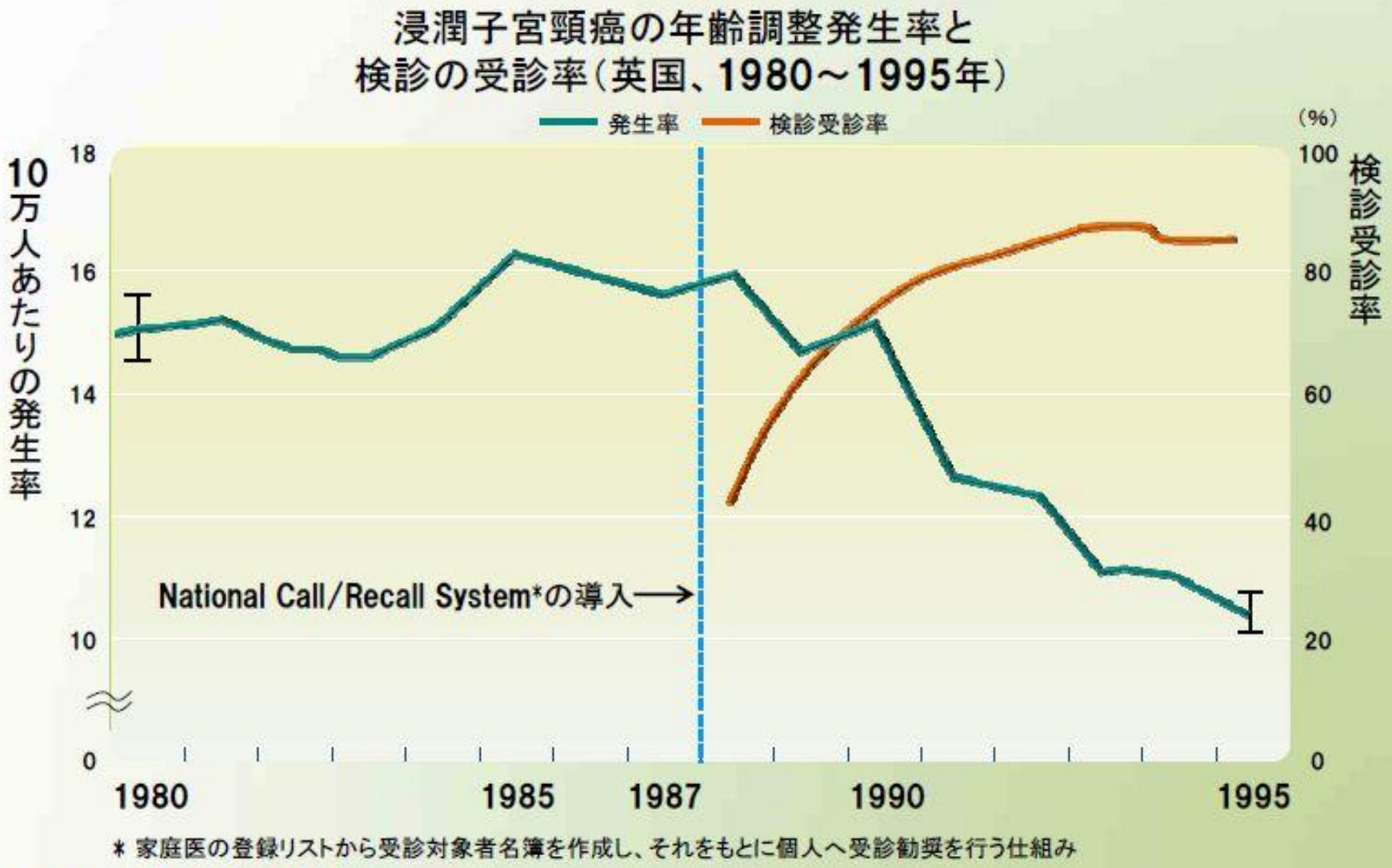
Early detection and early treatment

Very Low in Japanese cervial cancer screening rate



1 Programme data.
2 Survey data.
Health Care Quality Indicators Project. OECD 2009. OECD Health Data 2009 (cervical screening)

Invasive cervical cancer must be prevented by cc screening



Quinn M, Babb P, Jones J, Allen E. *BMJ*. 1999;318:904-908.
Adapted with permission from the BMJ Publishing Group.

http://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/cervical-cancer-screening （米国政府予防医療作業班）

Summary of Recommendations and Evidence

Cervical Cancer: Screening
Release Date: March 2012

Population	Recommendation	Grade (What's This?)
Women 21 to 65 (Pap Smear) or 30-65 (in combo with HPV testing)	The USPSTF recommends screening for cervical cancer in women age 21 to 65 years with cytology (Pap smear) every 3 years or, for women age 30 to 65 years who want to lengthen the screening interval, screening with a combination of cytology and human papillomavirus (HPV) testing every 5 years. See the Clinical Considerations for discussion of cytology method, HPV testing, screening interval.	A

21から65歳は3年に一度の細胞診、または、30から65歳では5年毎の細胞診＋HPVテストを推奨する
（⇔translation into Japanese）

that's all

Thank you for your attention