



Barts and The London  
School of Medicine and Dentistry

# Does what we know change what we do? Cervical screening and HPV testing

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## Outline

- From evidence to practice: some examples with timeline
- What we should expect from primary HPV testing

## Example 1: Cervical screening



### DIAGNOSIS OF UTERINE CANCER BY THE VAGINAL SMEAR

GEORGE N. PAPANICOLAOU, M.D., Ph.D.  
*Department of Anatomy, Cornell University Medical College*

AND

1943 HERBERT F. TRAUT, M.D.  
*Department of Obstetrics and Gynecology, Cornell  
University Medical College and the New York Hospital*

1956: Cervical screening in Birmingham (n=2500)

1965: 700,000 smears in England

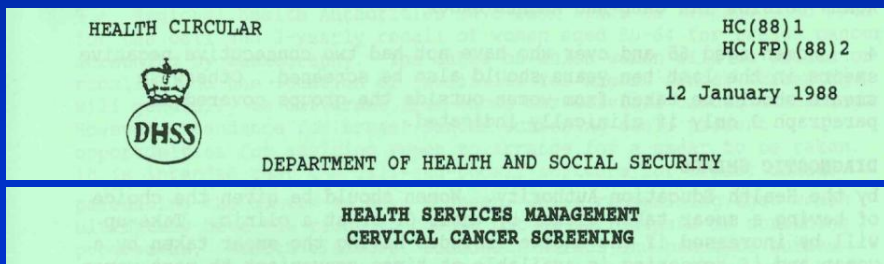
1975: 2.5 million smears in England

## BUT...

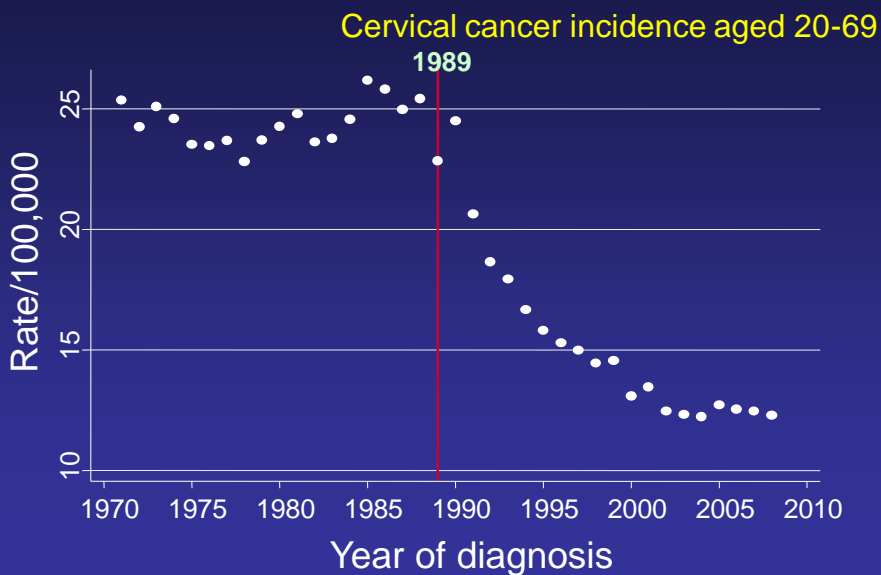
- 1972: Archie Cochrane: *“There are sins of omission and sins of commission. Of the latter the introduction of the programme of cervical smears in the hope of preventing carcinoma of the cervix is the saddest. It illustrates so clearly the consequences of assuming a hypothesis is correct, and translating the consequences into routine clinical practice before testing it by an RCT.”*

## Eventually what we know effects what we do

- 1984: ICRF report on organising a programme for cervical screening
- 1986: IARC publish observational evidence – screening can work
- 1988: Call-recall programme launched

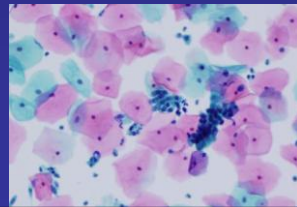


## What we do effects disease



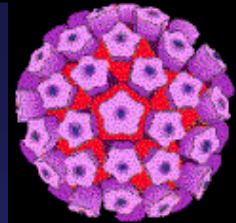
## Example 2: Liquid based cytology

- 1997: Canadian HTA reports on LBC
- 1999: HTA report
- 2000: NICE recommends LBC pilot
- 2001-03: LBC pilots
- October 2003: *LBC will be introduced across the CSP in England*
- October 2008: Roll-out completed



## Example 3: HPV triage

- 1999: Manos publishes
- 1999: TOMBOLA starts (MRC Funded)
- 2000: ALTS published
- 2001-03: HPV triage pilots
- 2004 Meta analysis published
- 2007: TOMBOLA publishes
- 2008: HPV Sentinel Sites
- 2011: Report on Sentinel sites published
- 2012: Roll-out of HPV triage starts



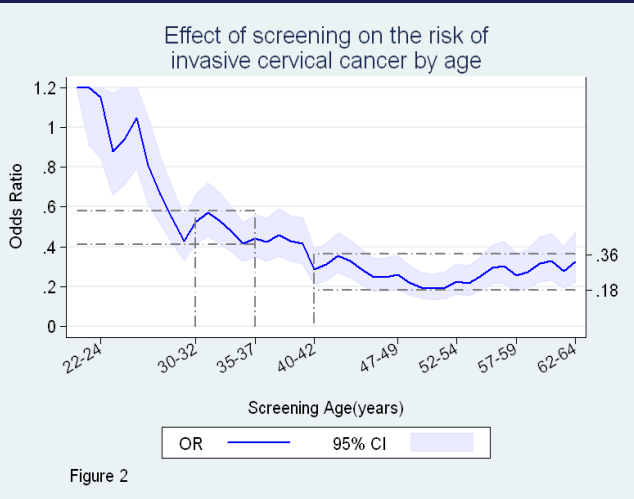
## Example 4: Age at first screen

- July 2003: Paper showing screening less effective in women age 20-39 recommending start at 25
- October 2003: New policy announced in England
- July 2009: New paper suggesting screening aged 20-24 is ineffective
- Jan 2011: N. Ireland invites from 25
- 2013: National Screening Committee (UK) recommends screening from 25

## Results from UK audit

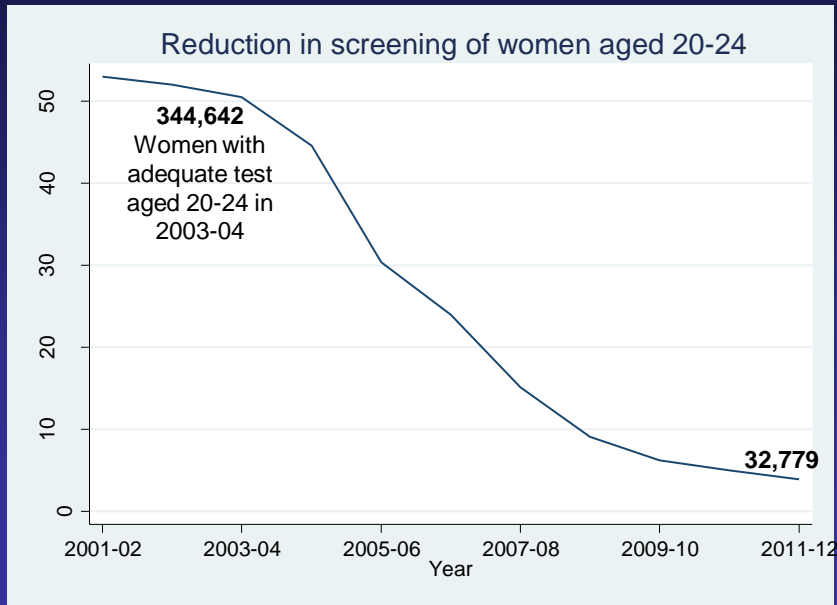
- 4012 cases aged 20-69
  - 1821 new since last publication
  - 73 aged 20-24
  - 351 aged 25-29

	OR
<b>Cancer diagnosed aged 25-29</b>	
Screened age 22-24	1.11 0.8-1.5
<b>Cancer diagnosed aged 35-39</b>	
Screened age 32-34	0.55 0.4-0.7
<b>Cancer diagnosed aged 45-49</b>	
Screened age 42-44	0.37 0.3-0.5



Sasieni, Castanon, Cuzick. *BMJ* 2009

## What we say effects what we do



## Example 5: HPV vaccination

- 2004, 2009: Bivalent vaccine results
- May 2007: Quadrivalent vaccine results
- Oct 2007: JVICI decision
- Sept 2008: HPV immunisation in UK

## Example 6: HPV testing in primary screening

- 1995: First study published
- 1999: HTA report
- 2002: Paper proposing HPV testing as the sole primary cervical screening test
- 2003: Multi-centre UK study published
- 2004: Baseline data from POBASCAM
- 2006: Over-view of cross-sectional studies
- 2006: ARTISTIC (negative), Italian RCT
- 2007: Swedish RCT

## Randomised trials – Second round

		CIN3+		Ratio HPV:Cyt
		HPV	Cytology	
Swedescreen <sup>1</sup>	3y	2.6 (+ C)	4.8 (C)	0.54
POBASCAM <sup>2</sup>	5y	2.9 (+ C)	6.4 (C)	0.45
ARTISTIC <sup>3</sup>	3y	1.9 (+ L)	3.6 (L)	0.51
NTCC <sup>4</sup>	3y	0.39 (± L)	0.71 (C)	0.55

1. Naucier et al, 2007    2. Bulkman et al, 2007    3. Kitchener, 2007    4. Ronco, 2010

## Example 6: HPV testing in primary screening (ctd)

- 1995: First study published
- 2006: Over-view of cross-sectional studies
- 2008: Long-term follow-up of HPV testing
- 2008: Proposal for controlled introduction
- 2010: Italian RCT shows reduction in cancer
- 2011: ATHENA trial, Routine US data
- 2012: Three US guidelines all approve HPV co-testing for women aged 20-65
- 2013: HPV pilot starts in women aged 25-64

## What would be lost if there were a 10 year delay in the roll out of HPV testing in primary screening?

- Reputation of cancer screening in the UK?
- Willingness of industry to support clinical trials in the UK?
- Women's lives?



## How much could primary HPV testing reduce cervical cancer incidence?

*J Med Screen 2013*

- 8760 women aged 25-64 with cervical cancer
- 17,341 individually matched controls
- Cervical cytology dates and results from 1988
- Negative cytology (resulting in routine recall) within 6 years of case-diagnosis
  - excluding tests within 0.5 years



*Poster #93*

## Definition: pre-cancer

- A woman who would develop (symptomatic or screen-detected) cervical cancer in the next six years (if not treated in the interim)

## Results (1)

Women aged 25-64

Test result (0.5-6.0 years)	Cases	Controls	OR	95%CI
≥1 negative	3400	12122	0.24	0.22-0.25
0 negative, ≥1 test	1185	1201	0.88	0.80-0.97
No tests	4175	4018	1.00	

OR estimated by conditional logistic regression

## Results (2)

Test result (0.5-6.0 years)	Cases
≥1 negative	38.8%
0 negative, ≥1 test	13.5%
No tests	47.7%

- Assuming 95% sensitivity to cytology negative pre-cancer
- 95% of 38.8% = **36.9%** of cases had a negative cytology but would have had a positive HPV test

## The nerdy slide

- 1000 women with pre-cancer
- 768 screened (coverage 76.8%)
- 590 screen positive on cytology (sensitivity 76.9%)
- 18 of these would be HPV negative (3% missed)
- 410 cancers NOT prevented by cytology
- $18/410 = 4.3\%$  extra cancers
  
- Net benefit of HPV testing =  $36.9\% - 4.3\% = 32.6\%$

## Cervical cancer in England aged 25-64

	Number	Rate/100,000
England 2010	1801	13.0
32.6% "preventable"	587	4.2
"Preventable" advanced cancers	123	0.9

- **Advanced cancer:**
  - FIGO stage 2+; or
  - Treated with radiotherapy or chemotherapy

## Impact of a 9 year delay in introducing HPV testing in primary screening

- Up to 5000 additional women getting cervical cancer
- 1100 women dying of cervical cancer under age 70



## Timelines

- 60 years from Papanicolaou to call-recall
- 4 years from HTA report to LBC roll-out
- 12 years from ALTS to HPV triage
- 16 months publication to HPV immunisation

## Does what we know effect what we do?

- Yes, but with a variable time-frame!

## What might be done?

- Plan from pilot to roll-out
- Review old decisions of funding bodies
  - Look at what was rejected too
- Rigorous evaluation with phased introduction
  - Cost differently
    - Compare to service (eg £170m pa for screening) not research (eg £500k pa for study)
  - Involve researchers in decision making despite conflict of interests
  - Encourage collaboration
  - Ease regulation – encourage innovation