

# **Limitations of HPV Testing**

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# Disclosure

I have no financial interest in any product in cervical cancer screening or other relationship with industry relative to the subject of this lecture.

# Limitations of HPV testing

- Leads to more positive tests, particularly at ends of the age spectrum
- Leads to new diagnoses of uncertainty: HPV+/cytology normal
- Identifies more CIN 1; more CIN 2
- Surveillance of women with uncertain diagnoses often leads to a cascade of events: overtreatment and adverse treatment outcomes
- Potential for adverse psychosexual effects when HPV testing is positive

# Goals

- Illustrate limitations using best evidence about trade-offs between benefits and harms of HPV testing
- Focus on head-to-head comparisons in primary screening: randomized trials of HPV testing (Hybrid Capture 2, HC2) *versus* cytology

# HPV Testing *versus* Cytology in Primary Screening: Randomized trials

HPV testing *added to* cytology:

- *passive* response to HPV+

UK, Italy

- *active* response to HPV+

Italy

HPV alone *versus* cytology

Italy

HPV alone with cytology triage *versus* cytology  
alone

Finland

(HPV alone *versus* control

India)

# Outcomes

## Cervical intraepithelial neoplasia (CIN)

- CIN 1: high spontaneous resolution
- CIN 2: most are treated, but about 40% resolve
- CIN 3: proximal cancer precursor
- AIS: widely considered a cancer precursor

**HPV testing added to cytology:  
- passive response to HPV+**

## HPV testing added to cytology: - passive response to HPV+

- UK, age 20-64, N=24,510 (no exclusion criteria stated)
- 2 screening rounds, 3 years apart
- Liquid-based cytology (LBC)  
*versus*  
Liquid-based cytology+HPV (LBC+HPV “revealed”)
- *Passive* response to HPV positivity  
Colposcopy for:
  - moderate dysplasia or worse (both arms)
  - persistent low-grade or worse cytology (LBC)
  - **persistent HPV+ in various scenarios (LBC+HPV)**
- Primary outcome: CIN 3+ in round 2

## HPV testing added to cytology: - passive response to HPV+

- Positivity rates (round 1):  
13% (LBC) vs. 22% (LBC+HPV) NB: age 20-64
- Colposcopy rates (rounds 1+2):  
6.4% (LBC) vs. 8.3% (LBC+HPV)
- Results  
Less CIN 3+ detected in round 2 with LBC+HPV (“small” effect)  
0.47% (LBC) and 0.25% (LBC+HPV)  $p=0.042^*$

Over 2 screening rounds, no difference in CIN3+ or CIN2+ detected.  
Though no overall reduced quality of life, decreased sexual satisfaction in the LBC+HPV arm.

- Conclusions:  
Adding HPV to cytology increased number of positive tests and colposcopies but did not detect more CIN2+ over 2 screening rounds.

## HPV testing added to cytology: - passive response to HPV+

- Italy, age 25-34, N= 11,810\* (not pregnant, no hysterectomy, no treatment for CIN in last 5 yrs)
- 2 phases; 2 rounds, 3 years apart
- Phase 1  
Conventional cytology (CC) n=5808  
*versus*  
Liquid-based cytology+HPV (LBC+HPV) n=6602
- Colposcopy for:  
CC: ASC-US or worse  
LBC+HPV: **LSIL+** or ASC **with continued HPV positivity**
- Primary outcome: CIN 2+ after randomization

\*Ronco et al: *Lancet Oncol* 2006; 7:547-55

†Ronco et al: *Lancet Oncol* Jan 19, 2010

## HPV testing added to cytology: - passive response to HPV+ (colposcopy)

- Positive rates\*  
4.0% (CC) vs. 17.3% (LBC+HPV) NB: age 25-34
- Results (N=11,810), 2 rounds†  
In the LBC+HPV arm, more CIN 1 and 2 but not more CIN 3+  
CIN 1 cases: 38 (CC) vs. 145 (LBC+HPV)\*  
CIN 2 cases: 20 (CC) vs. 58 (LBC+HPV)  
CIN 3/AIS cases: 30 (CC) vs. 31 (LBC+HPV)  
CIN 2+ cases: 50 (CC) vs. 89 (LBC+HPV)
- Conclusions:  
-compared to CC, LBC+HPV greatly increased the test positivity rate, found more CIN 1\* and more CIN 2 but not more CIN 3+

\*Ronco et al: *Lancet Oncol* 2006; 7:547-55

†Ronco et al: *Lancet Oncol* Jan 19, 2010

**HPV testing added to cytology:**  
**- active response to HPV+**  
**(colposcopy)**

## HPV testing added to cytology: - active response to HPV+ (colposcopy)

- Italy, age 35-60, (not pregnant, no hysterectomy, no treatment for CIN in last 5 yrs)
- 2 phases; 2 rounds, 3 years apart (N=68,835)
- Phase 1 (N=33,364)  
Conventional cytology (CC)  
*versus*  
Liquid-based cytology+HPV (LBC+HPV)
- Colposcopy for:  
CC: ASC-US or worse (except 2 of 9 centers)  
LBC+HPV: **ASC or worse** and/or HPV positive
- Primary outcome: CIN 2+ after randomization

## HPV testing added to cytology: - active response to HPV+ (colposcopy)

- Positive rates (round 1)\*  
3.8% (CC) vs. 10.6% (LBC+HPV) NB: age 35-60

- Results (N=33,364)

CIN 2:	36 (CC) vs. 64 (LBC+HPV)	RD 1.77
CIN 3/AIS:	34 (CC) vs. 55 (LBC+HPV)	RD 1.61
CIN 2/3/AIS:	70 (CC) vs. 118 (LBC+HPV)	RD 1.68

- Conclusions:
  - HPV plus LBC leads to more positive tests, more colposcopies and finds more CIN 2/3/AIS, more CIN 3/AIS<sup>†</sup> than conventional cytology alone

\*JNCI 2006 98:765

<sup>†</sup>Ronco et al: *Lancet Oncol* Jan 19, 2010

## HPV testing added to cytology: - active response to HPV+ (colposcopy)

Theoretic cohort of 1,000 women aged 35-60: estimated outcomes

	Cytology alone	Cytology plus HPV
<b>Tests</b>		
Cytology tests	1,000	1,000
HPV tests	0	1,000
<b>Invasive procedures*</b>		
Colposcopies	38	106
<b>Disease found†</b>		
CIN 2	2 (1.7)	4 (3.5)
CIN 3/AIS	2 (1.6)	3 (3.0)

\*based on baseline positivity rates

†after 1 round of screening

**For each additional case of CIN 3/AIS detected: 1,000 extra HPV tests and 68 extra colposcopies**

# **HPV alone *versus* cytology**

# HPV alone *versus* cytology

- Italy, age 35-60, N=35,471 (not pregnant, no hysterectomy, no treatment for CIN in last 5 yrs)
- 2 phases; 2 rounds, 3 years apart
- Phase 2:  
Conventional cytology (CC)  
*versus*  
HPV alone (HPV)
- Colposcopy for:  
CC: ASC-US or worse (except 2 of 9 centers)  
HPV: HPV positive
- Primary outcome: CIN 2+ after randomization

# HPV alone *versus* cytology

- Colposcopy referral rates (round 1)\*  
3.1% (CC) *vs.* 5.8% (HPV) NB: 7.1% in phase 1

- Results (n=35,471)  
Relative detection (RD): rounds 1+2

CIN 2 cases:	33 (CC) <i>vs.</i> 52 (HPV)	RD 1.58
CIN 3/AIS cases:	30 (CC) <i>vs.</i> 51 (HPV)	RD 1.70
CIN 2/3/AIS cases:	63 (CC) <i>vs.</i> 103 (HPV)	RD 1.64
Cancer cases:	15 (CC) <i>vs.</i> 6 (LBC+HPV/HPV)	$p=0.052$

- Conclusions:  
-HPV testing leads to more positive tests, more colposcopies and finds more CIN 2 and 3 than cytology; treatment of CIN 2+ may lead to less cancer

Ronco et al: *Lancet Oncol* Jan 19, 2010

\*Ronco et al: *JNCI* 2008;100:492-501

# HPV alone *versus* cytology

Theoretic cohort of 1,000 women aged 35-60: estimated outcomes

	Cytology alone	HPV alone
<b>Tests</b>		
Cytology tests	1,000	0
HPV tests	0	1,000
<b>Invasive procedures*</b>		
Colposcopies	31	58
<b>Disease found†</b>		
CIN 2	2 (1.5)	3 (2.8)
CIN 3/AIS	1 (1.1)	3 (2.7)

\*based on baseline positivity rates

†after 1 round of screening

**For each additional case of CIN 3/AIS detected: 17 extra colposcopies**

**HPV alone with cytology triage**  
*versus cytology*

# HPV alone with cytology triage *versus* cytology

- Finland, age 25-65, N=108,425
- One screening round reported
- Conventional cytology (CC)  
*versus*  
HPV with cytology triage (HPV->CC)
- Colposcopy for:  
CC: LSIL or worse  
HPV->CC arm: HPV positive plus abnormal cytology
- Primary outcome: CIN 1, 2, 3 or cancer

# HPV alone with cytology triage *versus* cytology

- Positive rates  
7.0% (CC) *vs.* 7.3% (HPV)  
Colposcopy referral 1.2% in both groups (LSIL+, HPV with cytology triage)
- Results (N=108,425)  
Relative sensitivity of HPV with cytology triage *versus* cytology  
CIN 1 1.44 (95% CI 0.99-2.10) 67 vs 46 cases  
CIN 2 1.39 (95% CI 1.03-1.88) 104 vs 74 cases  
CIN 3+ 1.22 (95% CI 0.78-1.92) 36 vs 30 cases
- Need for intensive follow-up  
CC arm: 6.6% *vs.* HPV->CC arm: 7.2% ( $p < 0.05$ )
- Conclusions:
  - HPV testing with cytology triage equal sensitivity for CIN 3+; more intensive follow-up needed with HPV testing compared to cytology alone
  - HPV testing leads to more CIN 2

# Limitations of HPV testing: effect of older age

High positivity rates in older women relative to disease prevalence (low positive predictive value)

## Finland

- 29,552 women aged 50-64
- 18 cases of CIN 3+ (prevalence 0.06%); NNS=1641

## UK

- 5,613 women aged 50-64 (round 1)
- 9 cases of CIN 3+ (prevalence 0.16%); NNS=624
- All with CIN 3+ were HPV positive; all had moderate or worse cytology
- HC2 positivity: 6.6% 371 women
- Cytology positivity (mod+): 0.4% 23 women

## Potential adverse effects of LEEP

Preterm delivery	70% increase
Low birth weight	82% increase
Preterm premature ROM	169% increase

*Lancet* 2006 367:489-98

## Potential severe adverse effects of cone biopsy (not LEEP or cryotherapy)

Perinatal mortality	187% increase
Severe preterm delivery	178% increase
Extreme low birthweight	186% increase

No randomized trials.

*BMJ* 2008 Sep 18;337

# Limitations of HPV testing

- More positive tests, particularly at ends of the age spectrum
- More uncertainty: HPV+/cytology normal
- More CIN 1 and CIN 2
- More surveillance: overtreatment and adverse treatment outcomes
- Potential adverse psychosexual effects

## **Burden of cervical cancer in the US: 2009**

- 80 million women at risk in the US
- 11,000 cases of cervical cancer
- 50-60% in poorly-screened women
- 30% in women despite adequate screening\*
- 4 per 100,000 US women per year

*\*Obstet Gynecol 94:307-10*

# Perspectives

- Many screening strategies are possible; individualization to setting and resources is critical.
- Screening: complex balancing of benefits and harms
- Multiple perspectives: public health officials, payers, industry, laboratories, cytologists, colposcopists, women

# Complexities

“It is a challenging time to be a clinician or health planner dedicated to cervical cancer prevention.

Even in the most wealthy regions, using vaccination, cytology, and HPV testing without careful planning would invite waste and, more importantly, overtreatment.”

-Mark Schiffman, Diane Solomon

*JAMA* 2009;302(16):1809-1810.

# Conclusions

Most cervical cancer occurs among women who have never been screened; providing easy access to affordable screening is the priority

With new technologies, must take care to not simply trade one uncertainty for others of a greater magnitude and with the potential for greater harm

Make guidelines to best fit the best balance of population benefits and harms, not guidelines to fit the characteristics of our current tests

We need *better* screening, not just *different* screening.

Be sure that “better” is principally and consistently defined from the perspective of women