FDA and Interim Guidance: HPV Primary Screening What, Why, and How?

Satellite Conference and Live Webcast
Thursday, June 25, 2015
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Produced by the Alabama Department of Public Health
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Faculty

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Disclosures

- **Consultant (Non-paid): Roche Molecular Systems**
- **Scientific Advisory Board: Merck (V503)**

Objectives

- **To review the benefits and known limitations of cervical cytology**
- **To review the scientific evidence in support of HPV testing as a primary screening test**
- **To review the role of cervical cancer screening in the era of HPV vaccination**

Topics to Cover

- **Cytology screening as the paradigm of cervical cancer control: Glory for some, failure for many**
- **Rationale and burden of proof for HPV DNA testing in primary screening for cervical cancer**
- **Post-HPV vaccination era: need for a paradigm change that combines primary and secondary prevention**

How Good is Pap Cytology in Cervical Cancer Screening?

- **Duke Report (Nanda et al., 2000): sensitivity 51%, specificity: 98%**
- **Pooled analysis of European and Canadian studies (Cuzick et al., 2006): sensitivity 53%, specificity 96%**
- **Cytology screening programs have to compensate for the low sensitivity by requiring 2-3 annual Pap tests before screening can be done less frequently**

How Good is Pap Cytology in Cervical Cancer Screening?

- Approximate program sensitivity for:
  - 2 consecutive annual Pap tests: 51% + 51% of 49% = 76%
  - 3 consecutive annual Pap tests: 76% + 51% of 24% = 88%

Other Issues to Consider with Cytology

- Highly subjective test: substantial inter - laboratory (as well as intra - laboratory) variability and limited reproducibility
- Unable to identify those women who are at future risk of developing cervical cancer precursors

Other Issues to Consider with Cytology

- Unclear how cytology will perform as HPV vaccination rates increase in the United States

HPV Testing in Cervical Cancer Screening

(For DNA of High Oncogenic Risk Types)

- Approaches already implemented or being evaluated:
  - Serial: Cytology screening followed by HPV testing to triage ASC-US (approved by many professional societies in North America, FDA)

HPV Testing in Cervical Cancer Screening

(For DNA of High Oncogenic Risk Types)

- Parallel: Cytology and HPV cotesting (approved by some professional societies in North America, FDA)
- Serial: HPV testing followed by cytologic triage (aka, Primary HPV Screening)

The Central Goal in Cervical Cancer Screening

- "All zoogles are boogles. You saw a boogle. Is it a zoogle?"
  - Question in an SAT exam (Nassim Nicholas Taleb in "The Black Swan")

The Central Goal in Cervical Cancer Screening

- All cervical cancers are caused by HR-HPV infection.
  - If a woman is positive on screening for HR-HPV DNA is precancer or cancer present or imminent?

The Central Goal in Cervical Cancer Screening

- Of all screening technologies, HPV DNA testing is the one with greatest sensitivity and negative predictive value
- Most important point: a negative result provides long-term confidence that a lesion is not present

Why is HPV DNA Testing an Attractive Option for Cervical Cancer Screening?

- More sensitive and reproducible than the Pap test
- More "upstream" in the carcinogenic process, thus enabling a longer safety margin for screening intervals
- Assesses future risk (and not just the presence of current disease)

Why is HPV DNA Testing an Attractive Option for Cervical Cancer Screening?

- Can be automated, centralized, and be quality - checked for large specimen throughput
- May be more cost - effective than cytology if deployed for high volume testing, such as in primary screening

Why is HPV DNA Testing an Attractive Option for Cervical Cancer Screening?

- A more logical choice for screening women vaccinated against HPV infection

RCTs of HPV Testing in Screening

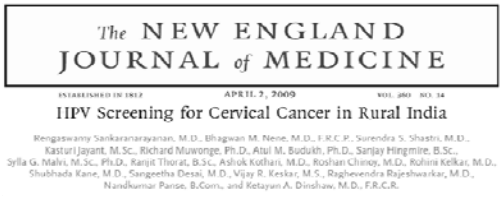
- POBASCAM study: The Netherlands (Meijer et al., Int J Cancer 2004; Bulkmans et al, Lancet 2007)
- Indian Trial (Osmanabad) (Sankaranarayanan et al. NEJM 2009)
- ARTISTIC trial: UK (Kitchener et al. Lancet Oncol 2009)

RCTs of HPV Testing in Screening

- NTCC Italian Study (Ronco et al., Lancet Oncol, 2006; JNCI 2006)
- SWEDESCREEN: Swedish trial (Elfgren et al. AJOG 2005; Naucler et al., NEJM 2007; JNCI 2009)
- Finnish RCT (Kotaniemi et al., BJC 2005; Eur J Cancer 2008; IJC 2008; Leinonen et al., JNCI 2009)

RCTs of HPV Testing in Screening

- CCCaST study: Canada (Mayrand et al., IJC 2006; NEJM 2007)
- BC RCT (HPV FOCAL): Canada (Ogilvie et al, BJC 2012)
- ATHENA Trial: United States

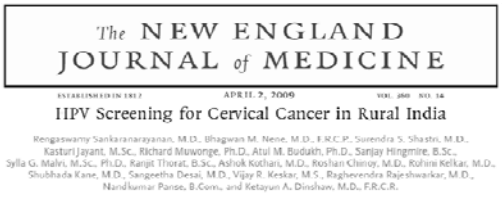

The NEW ENGLAND JOURNAL of MEDICINE

APRIL 2, 2009

HPV Screening for Cervical Cancer in Rural India

Rengaswamy Sankaranarayanan, M.D., Bhagwan M. Nene, M.D., F.R.C.P., Surendra S. Shastri, M.D., Kasturi Jayant, M.Sc., Richard Muwonge, Ph.D., Atul M. Budukh, Ph.D., Sanjay Hingmire, B.Sc., Sylla G. Malvi, M.Sc., Ph.D., Ranjit Thorat, B.Sc., Ashok Kothari, M.D., Roshan Chinoy, M.D., Rohini Kelkar, M.D., Shubhada Kane, M.D., Sangeetha Desai, M.D., Vijay R. Keskar, M.S., Raghevendra Rajeshwarkar, M.D., Nandkumar Panse, B.Com., and Ketayun A. Dinshaw, M.D., F.R.C.R.

- Site: Osmanabad district, India
- Cluster - randomized trial: 131,746 women aged 30 - 59 years randomly assigned to 4 groups of 13 clusters each
- Groups: Screening by HPV testing, cytology, VIA, control (standard care)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- Those with positive screening results underwent colposcopy and biopsies; treatment given to those with precancerous lesions or cancer

Risk of cervical cancer or precancer among 330,000 women undergoing concurrent HPV testing and Pap testing in routine clinical practice

Rate of Cervical Cancer Following a Negative HPV Test or Normal Pap Test

- For all women with normal Pap test:
  - 7.5 cervical cancers per 100,000 women / year
- For all women HPV - negative:
  - 3.8 cervical cancers per 100,000 women / year

Rate of Cervical Cancer Following a Negative HPV Test or Normal Pap Test

- For all women HPV - negative who also had a normal Pap test:
  - 3.2 cervical cancers per 100,000 women / year

Addressing the Need for Advanced HPV Diagnostics (ATHENA trial)

- 47,000 women enrolled
- Roche Cobas 4800: FDA approval for ASC-US triage and cotesting
- Unanimous approval for candidate primary HPV screening algorithm (13-0) on March 12, 2014

Is Screening Needed After Vaccination?

- Yes!!!
  - Vaccines protect against HPVs 16 and 18 which cause at most 75% of all cervical cancers
  - Vaccination is for pre - exposure prophylaxis; most women will continue to rely on screening

But How?

Perfect Political Storm in 2006

- qHPV vaccine approved by the Therapeutics Goods Administration
- Australian vaccine with an iconic inventor
- National Immunisation Program initially rejected it

Prof Ian Fraser

Perfect Political Storm in 2006

- Election year, with a budget surplus
- Health Minister with a dubious reputation in women's health

Perfect Political Storm in 2006

- First Lady with cancer of the cervix
  - De - stigmatized the disease
  - Influenced husband

John Howard Janette Howard

What are Vaccination Rates in the United States and Worldwide *Are We Making a Difference?*

- One of the highest HPV vaccination rates in the world: ~75% for the 3rd dose in 12 - 13 year olds
- From 2007 to 2011
  - Women <21 years old, 93% reduction in genital warts!

What are Vaccination Rates in the United States and Worldwide *Are We Making a Difference?*

- Women 21 - 30 years old, 73% reduction in genital warts
- No significant decline in women > 30 years old

What are Vaccination Rates in the United States and Worldwide *Are We Making a Difference? What About Men?*

- From 2007 to 2011
  - Substantial decline in warts in men, 50 - 80%, depending on age group (i.e., herd immunity)
  - No real decline seen in men (>30 years old)

Primary HPV Screening: Recommendations

- A negative hrHPV test provides greater reassurance of low CIN3+ risk than a negative pap (cytology) result
- Because of equivalent or superior effectiveness, primary hrHPV screening can be considered as an alternative to cytology based cervical cancer screening

Primary HPV Screening: Benefits

- More reproducible than Pap cytology
- Negative test (and most women will test negative) associated with very low risk of developing pre - cancer / invasive cancer (also, a much better predictor)
- More sensitive than cytology (lower FN rate): picks up most women with pre - cancers

Primary HPV Screening: Concerns

- Three screening options: more patient and provider confusion
- Unknown screening interval
- Comparison to co - testing?
- Over - treatment of women 25 - 29 years of age
- Missing cases where there is abnormal cytology yet a negative HPV result

Other Thoughts to Consider

- Data limited to women > 30 years of age
- Primary screening is most appropriate for organized screening programs that allow for referral of women to specialized programs that offer specific evaluation and treatment programs

Other Thoughts to Consider

- What is the best test to reflex to? Cytology, genotyping, biomarkers?
- Most studies are from Europe - one U.S. specific study (will be at least 4 - 5 years until the next one)

What Women (and Clinicians) Really Think About the Recent Guideline Changes

- Too confusing…. WT*
- Too many changes at once
- This is all about $$$
- Paps are going away…
- I am worried about increasing the screening intervals
- I cannot believe you are taking my pap away

References

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