Update on Cervical Cancer Screening

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Objectives

- Review the natural history of HPV as it relates to cervical cancer screening recommendations
- Review rationale behind current guidelines for cervical cancer screening
- Discuss key changes in the management of abnormal cervical cancer test results
- Discuss strategies to increase uptake of HPV vaccination in age appropriate young men and women
Cervical Cancer

- In the United States in 2012,
  - 12,170 new cases of invasive cervical cancer
  - 4,220 deaths

- Nationally, the lifetime probability of developing cervical cancer is 1:128

- The mean age for cervical cancer in the United States is 47 years
  - Peaks at 35 to 39 years and 60 to 64 years of age

- Inadequate screening in 60% of cases
  - 50 % never had cervical cytology testing
  - 10 % had no screening within 5 years

Natural history of Cervical Cancer

- Infection with specific high-risk strains of human papillomavirus (HPV) is central to the pathogenesis of cervical cancer
  - A necessary but not sufficient factor

- HPV genotype most important determinant of persistence
  - HPV-16 accounts for 55-60% of all cervical cancer
  - HPV-18 accounts for another 10% of all cervical cancer

- Other co-factors include smoking, compromised immune system, and HIV infection
• ~90% HPV infections are transient.

• Persistence of HPV infection for one and two years strongly predicts CIN 3.

• Untreated CIN 3 has a 30% probability of becoming invasive cancer over a 30 year period.
PREVALENCE OF HPV, CIN 3, AND CANCER BY AGE

Bosch et al. J Natl Cancer Inst Monogr. 2003;31:3-13
Burchell et al. Vaccine 2006;24 Suppl 3:S3/52-61
Cervical Topography
Screening Guidelines

American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology Screening Guidelines for the Prevention and Early Detection of Cervical Cancer

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1Director, Breast and Gynecologic Cancer, Cancer Control Science Department, American Cancer Society, Atlanta, GA, on behalf of the Steering Committee, Data Group, and Writing Committee; 2Senior Investigator, Division of Cancer Prevention, National Cancer Institute, National Institutes of Health, Rockville, MD, on behalf of the Steering Committee; 3Associate Professor, Department of Gynecology and Obstetrics, Emory University School of Medicine, Atlanta, GA, on behalf of the Data Group; 4Deputy Physician in Chief, Medical Director, Memorial Sloan-Kettering Cancer Center Regional Network, Department of Surgery, Gynecology Service, Memorial Sloan-Kettering Cancer Center,
Objectives of Screening Guidelines

- Prevent morbidity and mortality from cervical cancer
- Minimize potential harms associated with screening
Being rarely or never screened is the major contributing factor to most cervical cancer deaths today.

“Technologic improvements in screening are unlikely to have a substantial impact on mortality if they do not reach this population”

ASCCP 2012

- Who is not screened adequately?
  - Minorities
  - Low socioeconomic status
  - Foreign born
  - No usual source of health care
Retrospective Study of Cervical Cancer Diagnoses

- Pap results 3-36 months prior to diagnosis

N=833

- Failure to screen: 464 (56%)
  - No visit: 19%
  - 1-2 visits: 18%
  - >3 visits: 63%
- Failure in detection: 263 (32%)
- Failure to follow-up: 106 (13%)

Guidelines development process

- Topic areas to be addressed
  - Optimal cytology screening intervals
  - Screening strategies for women > 30 y/o
  - Management of discordant cytology and HPV results
  - Exiting women from screening
  - Impact of HPV vaccination
  - Potential for HPV testing as primary screening
Important principles that guided guideline development:

- Preventing all cervical cancer is unrealistic
- Reasonable risk is determined by a benchmark of the strategy of performing cytology alone at 2-3 yr interval
- Diagnoses with similar risk should be managed similarly
- CIN 3 is a reliable surrogate marker for sensitivity
- Risk of developing invasive cancer before next screen should be unlikely
- Harms of screening include anxiety, stigma of STI, pain/bleeding from procedures, and treatment related pregnancy complications
Guidelines did not address cervical cancer screening in special, high risk populations.
When to begin screening?

Cervical cancer screening should begin at age 21.

In adolescents,
- >90% HPV infections, LSIL, CIN 1 regressed in 3 years
- 60% of CIN 2 regressed in 3 years
- No data to support decreasing future rates of CIN 2 & 3 or cancer with screening
- Harm of treatment

### Cervical Cancer Incidence by Age Group, USCS*, 1998-2002

<table>
<thead>
<tr>
<th>Age</th>
<th>Rate per 100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-19</td>
<td>0.1</td>
</tr>
<tr>
<td>20-29</td>
<td>4.5</td>
</tr>
<tr>
<td>30-39</td>
<td>13.9</td>
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<tr>
<td>40-49</td>
<td>16.5</td>
</tr>
<tr>
<td>50-64</td>
<td>15.4</td>
</tr>
<tr>
<td>65+</td>
<td>14.6</td>
</tr>
<tr>
<td>All ages</td>
<td>9.4</td>
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</tbody>
</table>

United States Cancer Statistics includes data from CDC’s National Program of Cancer Registries and NCI’s Surveillance, Epidemiology and End Results Program.

Exceptions to the rule…

- HIV + women
  - ASCCP
    - Screening to start at 21 regardless of risk factors
  - CDC
    - Initiate screening at age of diagnosis, twice in the first year, then cytology annually
  - ACOG
    - Annual cytology starting at age 21 is “reasonable”
Screening for age 21-29

- Cytology every 3 years
  - No role for HPV in screening

- Why?
  - Change from annual to 3 year interval screening
    - Increase in lifetime number of cancers per 1000 women from $3/1000 \rightarrow 5-8/1000$
    - Decrease in lifetime colposcopy per 1000 women from $2000 / 1000 \text{ to } 760 / 1000$

- Most importantly:
  - Predicted lifetime risk of death with
    - Screening q 3 years 0.05
    - Screening q2 years 0.05
    - Screening q1 year 0.03

Screening for women ages 30-64

- Preferred
  - Cytology and HPV testing every 5 years

- Acceptable
  - Cytology every 3 years
Cytology screening alone versus co-testing

- Three randomized trials in Europe
  - Increase in detection of CIN 3+ (17-31%) with co-testing
  - Decrease in cancer detected at 2\(^{nd}\) round of screening (0.03%-0.05%) with co-testing

- Addition of HPV testing may enhance identification of adenocarcinoma of the cervix
Table 3. Evidence for Cotesting With HPV and Cytology vs Cytology Alone

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Main result</th>
<th>Number of studies</th>
<th>Quality of evidence</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIN3+</td>
<td>Absolute increase in detection of CIN3+ ranging from 17-31% in first round of screening</td>
<td>3 [39-41]</td>
<td>High</td>
<td>High-quality RCTs from Europe—indirectness based on population</td>
</tr>
<tr>
<td>Cancer incidence</td>
<td>Absolute decrease in cancer detected at 2nd round of 0.03-0.05%</td>
<td>2 [40, 41]</td>
<td>High</td>
<td>High-quality RCTs from Europe—indirectness based on population</td>
</tr>
<tr>
<td>Colposcopies</td>
<td>No direct evidence</td>
<td></td>
<td></td>
<td>Not reported in RCTs</td>
</tr>
<tr>
<td>Outcome</td>
<td>Main result</td>
<td>Number of studies</td>
<td>Quality of evidence</td>
<td>Comments</td>
</tr>
<tr>
<td>Cancer deaths (lifetime risk per 1000 women)</td>
<td>Decrease from 1.6-1.7/1000 to 1.4/1000</td>
<td>1&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Moderate-low</td>
<td>Modeling study, results consistent in sensitivity analysis using different inputs for sensitivity/specificity. Results consistent with other models showing relationship between sensitivity, specificity, and test frequency</td>
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<tr>
<td>Cancer incidence (lifetime risk per 1000 women)</td>
<td>Decrease from 8.5-8.9/1000 to 7.4-7.7/1000</td>
<td>1&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Moderate-low</td>
<td>Modeling study, results consistent in sensitivity analysis using different inputs for sensitivity/specificity. Results consistent with other models showing relationship between sensitivity, specificity, and test frequency</td>
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<td>Colposcopies (lifetime risk per 1000 women)</td>
<td>Decrease from 416-758/1000 to 323-573/1000</td>
<td>1&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Moderate-low</td>
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<sup>1</sup>Patients/population comprises women aged 30-65 years. The intervention was screening with cotesting (cytology and HPV), and the comparator was screening with cytology alone at the same interval.

<sup>2</sup>Patients/population comprises women aged 30-65 years. The intervention was screening with cotesting with HPV and cytology every 5 years, and the comparator was screening with cytology alone every 3 years.

<sup>3</sup>Unpublished data (Kulasingam, Shalini L. Personal correspondence, November 2011).
Problem of discordant results…

- HPV positive / cytology normal
- HPV negative / abnormal cytology
What do with HPV + / Cytology negative test?

- Occurs in 3.7% of women
- Repeat co-testing in 12 months
  - Or
- Immediate HPV genotyping
- COLPOSCOPY not indicated
What do with HPV + / Cytology negative test?

- Repeat co-testing in 12 months

- If HPV + or ASCUS + on repeat testing → Colposcopy
- If negative on both on repeat testing → Co-testing at 3 years is recommended
What do with HPV + / Cytology negative test?

- Repeat co-testing in 12 months
  - Or
- Immediate HPV genotyping

- If HPV 16/18 positive → Colposcopy
- If HPV 16/18 positive → Co-testing in one year is recommended
What to do with HPV - / ASCUS cytology?

- Repeat co-testing in 3 years if < 65
  - Based on KPNC data that showed CIN 3+ risk was comparable to negative cytology test results alone
- If 65 or older
  - Cannot exit testing
  - Repeat co-testing in 1 year
When to stop screening?

- Discontinue screening after age 65 in women with
  - Adequate negative prior screening results
    - Three consecutive negative cytology results
    - Two consecutive negative co-testing results
  - And No history of CIN 2 +
    - If positive history, continue to screen for 20 years

- Discontinue screening after total hysterectomy for benign indication and no history of CIN 2 +
Screening should not resume for any reason, even if woman reports having a new sexual partner.
Screening after HPV Vaccination

“Recommended screening practices should not change on the basis of HPV vaccination status”

- 30% of cervical cancers caused by other genotypes than HPV 16 & 18
- ACIP recommendations allow for vaccinations up to age 26
- Absence of vaccine registry
- Long term efficacy not established
2012 Updated Consensus Guidelines for the Management of Abnormal Cervical Cancer Screening Tests and Cancer Precursors

L. Stewart Massad, MD, Mark H. Einstein, MD, Warner K. Huh, MD, Hormuzd A. Katki, PhD, Walter K. Kinney, MD, Mark Schiffman, MD, Diane Solomon, MD, Nicolas Wentzensen, MD, and Herschel W. Lawson, MD,
for the 2012 ASCCP Consensus Guidelines Conference
From Washington University School of Medicine, St. Louis, Missouri; Albert Einstein College of Medicine, New York, New York; University of Alabama School of Medicine, Birmingham, Alabama; Division of Cancer Epidemiology and Genetics and Division of Cancer Prevention, National Cancer Institute, Bethesda, Maryland; The Permanente Medical Group, Sacramento, California; and Emory University School of Medicine, Atlanta, Georgia

- Routine screening revised / defined
- New data from KPNC cohort
- HPV testing more fully integrated
- Revised management guidelines for adolescents as well as 21-24 y/o
Box 1. Essential Changes From Prior Management Guidelines*

- Cytology reported as negative but lacking endocervical cells can be managed without early repeat.
- CIN 1 on endocervical curettage should be managed as CIN 1, not as a positive ECC.
- Cytology reported as unsatisfactory requires repeat even if HPV negative.
- Genotyping triages HPV-positive women with HPV type 16 or type 18 to earlier colposcopy only after negative cytology; colposcopy is indicated for all women with HPV and ASC-US, regardless of genotyping result.
- For ASC-US cytology, immediate colposcopy is not an option. The serial cytology option for ASC-US incorporates cytology at 12 months, not 6 months and 12 months, and then if negative, cytology every 3 years.
- HPV-negative and ASC-US results should be followed with co-testing at 3 years rather than 5 years.
- HPV-negative and ASC-US results are insufficient to allow exit from screening at age 65 years.
- The pathway to long-term follow-up of treated and untreated CIN 2+ is more clearly defined by incorporating co-testing.
- More strategies incorporate co-testing to reduce follow-up visits. Pap-only strategies are now limited to women younger than 30 years, but co-testing is expanded even to women younger than 30 years in some circumstances. Women aged 21-24 years are managed conservatively.

CIN, cervical intraepithelial neoplasia; ECC, endocervical curettage; HPV, human papillomavirus; ASC-US, atypical squamous cells of undetermined significance.

*Prior management guidelines were from the “2006 Consensus Guidelines for the Management of Women With Abnormal Cervical Screening Tests” (6). Prior guidelines not changed were retained.
When do you need to repeat pap?

- If cytology is unsatisfactory
  - Repeat testing in 2-4 months

- If cytology with absent or insufficient endocervical- TZ zone
  - Ages 21-29 → routine screening
  - Ages 30 + → Recommend HPV
    - HPV negative → routine screening
    - HPV positive → Co-test one year or genotype

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Management of Ages 21-24

- **ASCUS / LSIL**
  - Prefer repeat cytology at 12 months
  - Reflex HPV acceptable

- **HSIL**
  - Colposcopy
  - Immediate LEEP unacceptable

- **Young women**
  - Allows for discretion

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Barriers to adherence of guidelines:

- Lack of awareness of guidelines
- Rejecting of the evidence
- Care by anecdote
- Loss of pretext for health screening
- Concern for patient-clinician relationship
- Time constraints
- Concern of specific population
- Underestimation of harm of over-screening
- “Cook Book” medicine
- Medico-legal concerns
- Economic benefits / threats
- Industry marketing

Moscicki, 2010
HPV Vaccination

- Two FDA approved vaccines
  - Quadrivalent
    - HPV 6, 11, 16, 18
  - Bivalent
    - HPV 16, 18
- Targeted to female and males aged 11-12 years
- Catch-up vaccination recommended up to age 26 years

- Efficacy
  - 100% among participants who were naïve against vaccine genotype and followed protocol

- Safety
  - More than 57 million doses have been given with no data to suggest adverse reactions

- Only 33% of adolescent girls and less than 7% of boys in the US have completed the 3-dose series of either vaccine

Overall U.S. coverage among female adolescents is 33.4%.

Source: Centers for Disease Control and Prevention. National and state vaccination coverage among adolescents aged 13-17 years—United States, 2012. MMWR. 2013 Aug 30;62(34):685-93. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23985496. Data from National Immunization Survey-Teen (NIS-Teen) among female adolescents (N = 9,058) born between January 6, 1994, and February 18, 2000. Gardasil® or Cervarix® may have been received; more than the recommended three doses may have been received.
Increasing HPV vaccination

- Identify patients during catch-up period
- Educate mothers on importance of vaccinating children
- Educate on efficacy and safety
  - HPV vaccination in the recommended ages is not associated with increased sexual activity-related outcome rates.
  - Based on cohort of 1398 girls
- Maximize access to HPV vaccination services
- “Physician recommendations play a crucial role in the acceptance of HPV vaccination by patients and parents of patients.”

Factors Contributing to Providers’ Hesitancy
- Limited understanding of HPV-associated diseases and benefits of HPV vaccination, particularly for males
- Concerns about safety
- Concerns about inadequate reimbursement for vaccines
- Personal attitudes and beliefs
- Discomfort talking to parents and adolescents about a topic related to sexual behavior
- Concerns about parental resistance
- Preference for vaccinating older versus younger adolescents
- Lack of time or incentives to educate parents and patients about HPV and HPV vaccines
- Lack of systems to remind providers to offer vaccines to age-eligible patients

Reasons Parents Did Not Intend to Vaccinate Their Adolescents Against HPV
- Vaccination not needed, particularly for males
- Vaccination not recommended by healthcare provider
- Safety concerns
- Lack of knowledge about the vaccines or diseases caused by HPV infections
- Son or daughter not sexually active
- Son or daughter too young to be vaccinated against HPV
- Cost of vaccines
Human papillomaviruses (HPV) cause most cases of cervical cancer and large proportions of vaginal, vulvar, anal, penile, and oropharyngeal cancers. HPV also causes genital warts and recurrent respiratory papillomatosis. HPV vaccines could dramatically reduce the incidence of HPV-associated cancers and other conditions among both females and males, but uptake of the vaccines has fallen short of target levels. The President’s Cancer Panel finds underuse of HPV vaccines a serious but correctable threat to progress against cancer. In this report, the Panel presents four goals to increase HPV vaccine uptake: three of these focus on the United States and the fourth addresses ways the United States can help to increase global uptake of the vaccines. Several high-priority research questions related to HPV and HPV vaccines also are identified.

Click below to read more.

HOW TO ACCELERATE HPV VACCINE UPTAKE IN THE U.S.
Questions ?