New Cervical Cancer Guidelines: Perspectives by organizations, doctors, and women

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Annual NCCC Mtg
Atlanta, GA
January 19, 2013
Multiple centers and divisions involved with HPV and Cervical Cancer at CDC

- NCEZID HPV LAB
- NCCDPHP Cancer Screening and Cancer Surveillance
- NCEZID Immune Safety
- NCIRD Immunizations
- CGH Global Immunizations Pepfar
- NCHHSTP HPV Surveillance ACIP
Cervical Cancer in the United States

- **Burden**
  - ≈12,000 new cases, 7.4 per 100,000
    - Approximately 20-30% are adenocarcinomas
  - ≈4,000 deaths, 2.4 per 100,000
  - Hispanic and Black women at increased risk of getting and dying from cervical cancer

- **Screening**
  - HP 2020 target: 93% of women 21-65 should have a Pap test in past 3 years
  - 83% of women 21-65 report having a Pap test within past 3 years
  - Women 50-64 have lowest rates of screening
  - Black women and white women similar rates of screening
  - Hispanic women and Asian women lower rates
  - Foreign-born lower rates
Cervical Cancer Rates by State, 2004-2008

Screening Failures

- Among women who have never been screened
  - 50-60%

- Among women not screened in the past 5 years
  - 10%

- Among women lost to followup
  - 10%

- Among errors in samples and interpretation
  - 30%
Screening Principles

- Want to prevent morbidity and mortality from cervical cancer
- Benefits should outweigh harms
- Average-risk, Asymptomatic population
# New Cervical Cancer Screening Guidelines

<table>
<thead>
<tr>
<th></th>
<th>ACS 2012</th>
<th>USPSTF 2012</th>
<th>ACOG 2012</th>
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</thead>
<tbody>
<tr>
<td><strong>Age to start</strong></td>
<td>Age 21</td>
<td>Age 21</td>
<td>Age 21</td>
</tr>
<tr>
<td><strong>Women ages 21-29</strong></td>
<td>Cytology every 3 years</td>
<td>Cytology every 3 years</td>
<td>Cytology every 3 years</td>
</tr>
<tr>
<td><strong>Women ages 30-65</strong></td>
<td>Cotesting every 5 years (preferred) or Every 3 years with Pap alone</td>
<td>Cotesting every 5 years or Every 3 years with Pap alone</td>
<td>Cotesting every 5 years (preferred) or Every 3 years with Pap alone</td>
</tr>
<tr>
<td><strong>Women ages &gt;65</strong></td>
<td>Discontinue after age 65 years (adequate screen)</td>
<td>Discontinue after age 65 years</td>
<td>Discontinue at age 65 years (adequate screen)</td>
</tr>
<tr>
<td><strong>Total Hysterectomy</strong></td>
<td>Discontinue (if no history of CIN2+)</td>
<td>Discontinue (if no history of CIN2+)</td>
<td>Discontinue (if no history of CIN2+)</td>
</tr>
<tr>
<td><strong>Screening among fully vaccinated</strong></td>
<td>Same as for non-vaccinated</td>
<td>Not reviewed</td>
<td>Same as for non-vaccinated</td>
</tr>
</tbody>
</table>
The “annual” Pap test is dead!

A PAP TEST FOR EVERY WOMAN EVERY YEAR!

-American Cancer Society 1957
How much protection do we lose by not doing Pap tests every year?

- Percentage reduction in rate of invasive cervical cancer in cohort of women aged 35 - 64 with different frequencies of screening
- Assumes at least negative Pap prior to age 35
  - Next Pap 1 yr: 93.5%
    - 30 Paps required over 30 years
  - Next Pap 2 yrs: 92.5%
    - 15 Paps required over 30 years
  - Next Pap 3 yrs: 90.8%
    - 10 Paps required over 30 years
  - Next Pap 5 yrs: 83.6%
    - 8 Paps required over 30 years

IARC Br. Med Jl. 293:1986
What are the harms of abandoning annual screening?

- Markov model based on NBCCEDP data
- Assumed ≥3 prior consecutive negative Paps
- Cancers prevented by doing Pap annually instead of every 3 years
  - Age 30 – 44: 3 / 100,000 women
  - Age 45 – 59: 1 / 100,000 women
- Additional tests needed to find each incremental cancer
  - Age 30 – 44: 69,665 Paps plus 3,861 colpos
  - Age 45-59: 209,324 Paps plus 11,502 colpos

Sawaya et.al. NEJM 2003;349:1501-9
Age to start is now 21 years

- Women under 21 should not be screened regardless of sexual onset
- HPV is common after sexual onset
- Cervical cancer is rare in women under 25 years of age
- Harms outweigh the benefits
  - An abnormal Pap and low-grade precancers can trigger LEEP
  - Leeps have increase risk of reproductive health outcomes
    - Preterm birth
    - Low birthweight
    - Premature Rupture of Membranes
- Canadian Task Force recommending age 25 to start screening
Cervical Cancer is Rare among Young Women

- 0.1% of cervical cancers in U.S.
- Rate 1.5/1,000,000
  - Ave 14 cancers per year
  - Too rare to report under age 15
  - Age 20-24: 125 cancers per year (14 / million)

- ~2,737,000 Paps done per year age 15-19
  - 200,000 Pap tests per cancer
    - At $60 per Pap = $11,646,800 per cancer
  - Age 35-39: 4,921 Paps at 300-375K per cancer

Benard et al, Obstetrics and Gynecology
Pap, No HPV testing in women under 21-29?

- Cytology every 3 years
- HPV testing should not be used for screening
Prevalence of HPV 6, 11, 16, 18 among females, NHANES, 2003-2006
Happy 30\textsuperscript{th} Birthday!

What Test Will be on the Menu and What Test Will You Have?

I prefer the HPV and the Pap test every 5 years

I'll have the pap smear.

every 3 years

I prefer the HPV and the Pap test every 5 years
HPV Co-testing and 5 year Intervals

- Recommended for women 30-64 years old
- Co-testing leads to earlier diagnosis of CIN 3+ and Cancer
- Incorporating HPV finds more AIS than cytology alone
- Negative cytology plus negative HPV allows spacing screening beyond every three years.
- More women will have HPV+ test, normal cytology that will need closer surveillance
Follow-up of 5 yrs of Co-testing Kaiser N Cal.

More CIN 3+ diagnosed by HPV than Pap within 2 years – almost doubled by 5 years.

Follow-up with repeat co-testing in one year per 2006 ASCCP Guidelines.

5 yr cumulative CIN 3+ in >300,000 women

**Positive HPV diagnoses more AIS and Adenocarcinoma than Cytology alone**

331,818 women enrolled in Kaiser N. Cal

Significantly more AIS and Adenoca diagnosed over 5 yrs if initial screen:

- HPV + vs Pap + $\quad (p<0.0001)$
- HPV + / Pap – vs HPV -- / Pap + $\quad (p<0.0001)$

<table>
<thead>
<tr>
<th></th>
<th>AIS</th>
<th>Adenocarcinoma</th>
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<tbody>
<tr>
<td>Total</td>
<td>70</td>
<td>27</td>
</tr>
<tr>
<td>Pap Negative</td>
<td>42 (60%)</td>
<td>23 (85%)</td>
</tr>
<tr>
<td>Pap Positive</td>
<td>28 (40%)</td>
<td>4 (15%)</td>
</tr>
<tr>
<td>HPV Positive</td>
<td>56 (80%)</td>
<td>21 (78%)</td>
</tr>
<tr>
<td>Pap -- / HPV +</td>
<td>31 (44%)</td>
<td>17 (63%)</td>
</tr>
<tr>
<td>Pap + / HPV --</td>
<td>3 (4%)</td>
<td>0</td>
</tr>
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</table>

A negative HPV DNA test offers better protection after 6 years than a negative Pap does after 3 years.

- Joint European Cohort Study compared HPV testing with conventional Pap in 6 countries
- N=24,295

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<thead>
<tr>
<th></th>
<th>3 yrs</th>
<th>4 yrs</th>
<th>5 yrs</th>
<th>6 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pap –</td>
<td>0.51%</td>
<td>0.69%</td>
<td>0.83%</td>
<td>0.97%</td>
</tr>
<tr>
<td>HPV-</td>
<td>0.12%</td>
<td>0.19%</td>
<td>0.25%</td>
<td>0.27%</td>
</tr>
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Dillner, J. et al. BMJ 2008;337:a1754
Why didn’t guidelines in United States change for screening among vaccinated?

- **Low vaccine coverage**
  - Lower completion rates
  - Unclear if vaccination is occurring before sexual debut

- **Opportunistic Screening**

- **Medical Records don’t connect**
  - Screeners don’t see vaccination records or screening history

- **Waiting to see actual impact on lesions/disease vs. modeling**

- **Individual vs. Population-based**
Predicted reduction in CIN3 among 20- to 29-year-olds after onset of HPV vaccination based on US data

Lower coverage scenario
3-dose coverage 30% at age 12, ~ 50% by age 26

Higher coverage scenario
3-dose coverage 75% at age 12, ~ 90% by age 26

Based on model of Chesson et al (Vaccine 2011) and includes indirect effects (herd immunity). The model assumed 95% efficacy against HPV 16/18, with no cross-protection. HPV 16/18 were assumed to account for 58.6% of CIN3.
Future Screening needs to be more in light of HPV vaccination

Vaccination

- Decreased HPV prevalence (HPV 16/18)
- Pap test characteristics will be affected
- Decrease in procedures
- Change strategy to HPV-based screening
Cervical Cancer Screening Still Needs to Continue

Stopping Screening?

- Adequately screened women with a cervix age 65
- Hysterectomy
- Women with history of CIN2+ need routine screening for 20 years
WOMEN’S BEHAVIORS
Trends in Pap testing among women 18-21 years, Behavioral Risk Factor Surveillance Survey (BRFSS), U.S. 2000-2010

- Never had Pap (18-21 yr)†
- Pap w/in 12 months (18-21 yrs)†
- Pap w/in 13-36 months (18-21 yr)†

Houston et al, MMWR 2013
How do Women feel?

- More women think a Pap test screens for more than it does
- Many women don’t know difference between Pap and Pelvic
- Having a Pap test once a year was the most widely accepted and preferred screening option
  - Approximately 14% felt Pap every 3 years acceptable
  - Approximately 8% felt Pap and HPV ever 5 years acceptable
- Women were least accepting of not having their Pap test until age 21 years
- Women over age 60 years were more accepting of stopping screening at age 65 than younger women

2012 Healthy Styles Survey, 1759 women
PROVIDER SURVEYS
Provider Surveys

- **Prior to new guidelines**
  - Guideline inconsistent screening common
  - Annual screening common in three different CDC Surveys

- **Now**
  - HPV co-testing was the most popular cervical cancer screening test recommendation
  - The most common screening interval was every 3 years
  - Most clinicians started recommending Pap tests at age 21
DISPARITIES
By State: HPV Vaccine Uptake/Cervical Cancer Death Rates

Low Mortality/High Uptake

High Mortality/Low Uptake
Estimated ≥ 1 Dose
HPV Vaccine Coverage,
Females 13-17 Years
National Immunization Survey 2010

<table>
<thead>
<tr>
<th>Category</th>
<th>Total US</th>
<th>At or Above Poverty</th>
<th>Below Poverty</th>
<th>Unknown Poverty</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>52%</td>
<td>50%</td>
<td>50%</td>
<td>50%</td>
</tr>
<tr>
<td>White</td>
<td>50%</td>
<td>50%</td>
<td>50%</td>
<td>50%</td>
</tr>
<tr>
<td>Black</td>
<td>50%</td>
<td>50%</td>
<td>50%</td>
<td>50%</td>
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<tr>
<td>Hispanic</td>
<td>50%</td>
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<tr>
<td>AI/AN</td>
<td>50%</td>
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<td>50%</td>
<td>50%</td>
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<tr>
<td>Asian/PI</td>
<td>50%</td>
<td>50%</td>
<td>50%</td>
<td>50%</td>
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Estimated 3 Dose HPV Vaccine Coverage, Females 13-17 Years
National Immunization Survey 2010

- Total US
- At or Above Poverty
- Below Poverty
- Unknown Poverty

Percentage by Race/Ethnicity:
- Overall
- White
- Black
- Hispanic
- AI/AN
- Asian/PI
SURVEILLANCE
New Screening Guidelines in Other Countries

- **Canada**
  - Start age at 25
  - Cytology every 3 years 25-69
  - NO recommendation of HPV testing yet
  - Will not recommend HPV co-testing

- **England**
  - Currently screening at age 25 since 2003
  - Moving towards HPV-based testing (pilot)

- **Scotland, Wales, N Ireland**
  - Considering changing screening age to 25

- **WHO guidelines (2014)**
  - Screen once in a lifetime between ages 30-49
  - VIA, HPV, cytology
What about for HPV vaccinated girls?

- **Australia**-
  - High vaccine coverage
  - Currently have the youngest age to start screening (18) and screen every 2 years
  - Established HPV vaccine registry
  - Existing Pap test registry

- **England**-
  - High vaccine coverage
  - Currently screening at age 25
  - Established screening registry
Change is coming

- **Australia**
  - Formal review of screening announced: ‘Renewal’ (includes consideration of primary HPV screening)
  - Literature review (Renewal Stage 1) and cost-effectiveness modelling of new technologies (Renewal Stage 2) due to be completed and report released end-2013
  - Stages 3 and 4 (data and quality systems and patient acceptability evaluations) due to be completed 2014
  - In parallel, investigator-initiated COMPASS trial of primary HPV vs. cytology is due to recruit 100,000 women from 2013-15 – will act as sentinel experience for HPV testing

- **United Kingdom**
  - Cost-effectiveness modelling of primary HPV screening in England, based on data from ARTISTIC trial, has been completed
    - Funded by the NHS National Cervical Screening Program
    - Planning pilot evaluations of primary HPV screening in areas already using HPV as triage test

*Courtesy Karen Canfe*
What can you as a cervical cancer survivor do?

- Encourage HPV vaccination for age-elegible men and women
- Support the new Cervical cancer screening guidelines
  - Realize that HPV co-testing is promising but may not fit all needs
  - Women who want more frequent screening (cytology)
  - Mobile populations
- Less cervical cancer screening doesn’t mean less care
- Highlight the horses and the zebras
- Destigmatize HPV and Cervical Cancer Screening
- Affordable Health Care Act & Electronic Medical Records
- Surveillance
  - Screening, Vaccine Registries
  - How many women that get cervical cancer are never/rarely screened
“The best strategy for preventing cervical cancer is to use the most accurate test at the longest possible interval.” - Jack Cuzick
Acknowledgements

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Lauri Markowitz, CDC

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