Preventing Cervical Cancer in 2012

Sarah Feldman MD MPH
Director Center for Pre-Invasive Disease of the Lower Genital Tract
Co-Director Ambulatory Gynecologic Oncology
Brigham & Women's Hospital
Dana Farber Cancer Institute
Harvard Medical School

Financial Disclosures

- none

Objectives

- Be familiar with new screening recommendations
- Understand the data behind the guidelines
- Learn how HPV testing may be used

Cervical Cancer--2011

- The etiology of cervical cancer is known (HPV)
- HPV infections are usually transient and low risk
- There is a long precancerous phase
- There are reasonable screening tests
- We have treatments that prevent progression of precancers
- HPV vaccine technology is rapidly progressing to the point that we may eventually be able to drastically reduce the prevalence of HPV disease.

WE SHOULD BE ABLE TO ERADICATE CERVICAL CANCER.

The scope of the problem....
Estimated Annual Incidence of HPV Cervical Infection/ Dysplasia

<table>
<thead>
<tr>
<th>Cervical Infection/ Dysplasia</th>
<th>United States</th>
<th>Worldwide</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV infection without detectable cytologic abnormalities</td>
<td>10 million</td>
<td>300 million</td>
</tr>
<tr>
<td>Low-grade dysplasia</td>
<td>1 million</td>
<td>30 million</td>
</tr>
<tr>
<td>High-grade dysplasia</td>
<td>300,000</td>
<td>10 million</td>
</tr>
</tbody>
</table>

- Virtually all cases of cervical cancer come from high-grade dysplasias. Low grade are not considered precancers.
- 50-80% women will test positive for the HRHPV at some point.

Prevalance of HPV Infection among US females

- 14-59 years old
- Self collected vaginal swabs
- HPV prevalence overall 24.5%
- 14-19: 25%
- 20-24: 45%
- 25-29: 28%
- 30-39: 25%
- 50-59: 20%
- HPV 16: 1.5%; HPV 18: 1.5% overall

Duration of HPV infections in young women

- Women aged 16-23
- Studied incidence and duration of HPV 6, 11,16 and 18 infection
- Mean duration of 6/11 approx 8 months
- Mean duration of 16/18 approx 14.5 months
- HPV 16/18 persists 2x as long on average as HPV 6/11

Natural History of HPV Infections

- Linked to presence of high risk/oncogenic HPV
- Lower levels of dysplasia may regress
- Higher levels of dysplasia are more likely to progress to cancer
- Smoking increases risk of cervical dysplasia

Natural History of CIN/ dysplasia

- Lesions may change over time
- Special populations differ with respect to risk of progression/regression (ie. Adolescents, pregnant, immunocompromised)
- Fertility desires may affect relative risk of treatment versus observation
- The data is complicated and constantly changing

Estimated Annual Incidence of HPV Cervical Infection/ Dysplasia

<table>
<thead>
<tr>
<th>Cervical Infection/ Dysplasia</th>
<th>United States</th>
<th>Worldwide</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV infection without detectable cytologic abnormalities</td>
<td>10 million</td>
<td>300 million</td>
</tr>
<tr>
<td>Low-grade dysplasia</td>
<td>1 million</td>
<td>30 million</td>
</tr>
<tr>
<td>High-grade dysplasia</td>
<td>300,000</td>
<td>10 million</td>
</tr>
</tbody>
</table>

Prevalance of HPV Infection among US females

- 14-59 years old
- Self collected vaginal swabs
- HPV prevalence overall 24.5%
- 14-19: 25%
- 20-24: 45%
- 25-29: 28%
- 30-39: 25%
- 50-59: 20%
- HPV 16: 1.5%; HPV 18: 1.5% overall

Duration of HPV infections in young women

- Women aged 16-23
- Studied incidence and duration of HPV 6, 11,16 and 18 infection
- Mean duration of 6/11 approx 8 months
- Mean duration of 16/18 approx 14.5 months
- HPV 16/18 persists 2x as long on average as HPV 6/11

Natural History of HPV Infections

- Linked to presence of high risk/oncogenic HPV
- Lower levels of dysplasia may regress
- Higher levels of dysplasia are more likely to progress to cancer
- Smoking increases risk of cervical dysplasia

Natural History of CIN/ dysplasia

- Lesions may change over time
- Special populations differ with respect to risk of progression/regression (ie. Adolescents, pregnant, immunocompromised)
- Fertility desires may affect relative risk of treatment versus observation
- The data is complicated and constantly changing
Long Term Risk of CIN3+ after HPV infection: role of persistence


- 8656 women in Denmark
- underwent pap and HC2 testing
- 2 exams, two years apart
- Estimated risk of CIN3+ for women who were HPV 16+ at both exams=47.4% (over 12 years of f/u)
- Risk of CIN3+ after HPV negative= 3%

Suggests less frequent follow up appropriate for HPV negative women, and aggressive follow-up should be considered for those persistently positive for HPV 16.

Making sense of the New Cervical-Cancer Screening Guidelines


Effectiveness of Prior guidelines

- Easy to remember
- Linked to other health care services
- Linked to life events
- Frequency of repetition improved sensitivity of otherwise not great tests

Evidenced Based Guidelines: Why cant they all agree?

- Expert committees agree on the “evidence”
- Areas where no “evidence” exists rely on “expert opinion”
- “Experts” have different areas of expertise and experience (i.e. public health, individual patient, primary care, oncologist)
- Well informed committees may still differ on interpretation and conclusions

Guideline Development Process 2011-2012

- Evidence reviewed and preliminary draft guidelines published fall 2011.
- Guidelines posted online and comments invited
- Committees reconvened to consider feedback and address new data
- March 2012 final guidelines published

2012 New Guidelines for Cervical Cancer Screening

3/ 14/ 2012 ACS, ASCCP, ASCP (www.ASCCP.org) USPSTF (www.USPSTF.org) Reviewed similar data

- Evidence Based
- Logical, simple to understand and clearly written
- Clearly address areas of patient and provider confusion
- AGREE !
## Cervical Cancer Screening Guidelines 2012

- For healthy women, initiate screening at 21, regardless of sexual activity.
- End screening at age 65 in well screened women (defined as 3 negative Paps or two negative co-screens within the past 10 years); poorly screened women still need to be screened in this age group.
- For healthy women age 30 and over with normal and adequate screening history, screening can be either with Pap alone q 3 years or Pap with HPV (cotesting) q 5 years if both results negative.

## Women at increased risk need more frequent screening

- HIV infected (screen 2x in first year and then annually if normal)
- Women who are immunosuppressed (e.g., organ transplants, chronic steroids or immunosuppressive drugs, auto-immune illnesses, etc)
- Women with a h/o DES exposure
- Women previously treated for CIN2/CIN3 or cancer. For this group, annual screening should occur for at least 20 years.
- Women with a h/o mildly abnormal Paps should probably still be followed closely.

## Additional Comments on Cervical Cancer Screening Guidelines 2012 (low risk women only)

- Discontinue screening after hysterectomy (including removal of the cervix) in women with no h/o cancer or dysplasia.
- HPV should not be used for screening in women under age 30.
- Vaccinated women should still be screened.

## Warning!

- These recommendations apply to average risk women and are not appropriate for women who have a history of high grade precancer or cervical cancer, are immunosuppressed or are DES exposed.

## Age to stop screening

- Highest rates of cervical cancer are in older women.
- Women who have not been screened or who have prior abnormal cytology should continue screening
- Women aged 65 with at least 3 negative Paps within the last 10 years may discontinue screening

## When to discontinue screening after hysterectomy?

- Women who have had a total hysterectomy for benign reasons and have no prior h/o CIN may discontinue screening
- Women with a h/o CIN2/CIN3 should continue screening
- Women for whom a negative history cannot be documented should continue screening
- The decision to discontinue testing should include both a review of the patient's Pap results prior to hyst and a pathologic confirmation of the hysterectomy specimen
HPV testing: how to incorporate into screening

HPV Typing: Clinical Utility
- Greater than 100 types
- Only "high-risk" types important
- Common infection—only persistent infections of concern
- More easily cleared in young women

HPV testing
- Hybrid Capture 2 tests for 13 high- and intermediate-risk HPV types—but may cross-react with low-risk types
- Cervista HR tests for 14 high/intermediate types
- Cervista HPV 16/18 tests for HPV 16/18—to be used only in women over 30
- Cobas 4800 HPV DNA test (Roche)
- Aptima miRNA HPV test (Genprobe)

DNA PAP Test
- FDA-approved (2003) for women over age 30 for primary screening
- No role for women under age 30
- Women who test negative on both are at low risk of developing cervical cancer over 3 - 5 years (Kaiser: 1996, Rijkaart DC: 2012, Katki: HA 2011)

Use of HPV testing
- Use for ASCUS patients 21 and over for triage (i.e. “reflex” testing)
- No use for screening (i.e. co-testing with Pap and HPV) before age 30
- For women age 30 and over Pap/HPV co-testing may be used every 5 years as an alternative to pap alone every 3 years, if results are normal.
- Current US guidelines do not support primary screen with HPV alone, or for any reason in women younger than 21.

What is the role of screening with HPV in a vaccinated population?  
- Expert forum 2008
- Estimate reduction in LSIL by 40-50% for vaccinated women-> makes Pap even less sensitive
- Safety of negative HPV test after 4 years is similar to a Pap after 1 year
- HPV 16/18 could be used in women>=30 for triage to Pap or Colposcopy
- Still unclear how to change screening recommendations for vaccinated women: for now these recommendations are the same as for unvaccinated women.
Management of Abnormal Screening Results (see www.asccp.org)

- Teens should not be screened. If screened and LSIL or ASCUS, repeat cytology in one year or at age 21. Patients with HSIL or AIS/AGC do need colposcopy.
- For patients aged 21 and over, refer for colposcopy all abnormalities (ASCUS HPV+, LSIL, HSIL, AGC, ca) except ASCUS HPV negative, which can be rechecked in one year.
- Do not delay evaluation of abnormal Paps, as with less frequent screening, each Pap abnormality is more likely to represent a true abnormal

Use of HPV genotyping in women aged 30+

- If pap-/HRhpv- → rescreen 5 years
- If pap-/HRhpv+ → may recheck cotest in 1 year OR may check hpv16/18
- If hpv16/18- → recheck pap, HRhpv in 1 year:
  - if both neg—→ rescreen 3 years
  - If pap-/HRhpv+→ colpo
  - If pap abnormal→ colpo

Will we be able to primarily screen with HPV?

Primary HPV screening

- Canadian Screening Trial (NEJM 2007)
  >10,000 women age 30-69
  Hc2 and conventional pap
- Dutch Randomized Screening Trial (Lancet 2007)
  17,000 women age 29-56
  Conventional pap or pap/pcr HPV

Results show similar overall detection of dysplasia, but HPV may detect earlier, but with higher percent of women undergoing colposcopy

Will need further study.....

Future uses of HPV testing

- HPV 16/18 account for 77% cervical cancers and 54% high grade lesions in US
- As successive cohorts are vaccinated, fewer women will get these infections
- Fewer Pap abnormalities will be detected
- Primary screening with HPV and triage to cytology might be the logical next step
- Still needs study

Bottom-line HPV info:

- Very common infection
- Most infections resolve—only persistent infections significant
- Infections in teens usually resolve
- Sexually transmitted—skin to skin contact
- Condoms do not fully protect against HPV, although may decrease risk of cervical cancer
- No role for primary screening below age 30
- In future, may screen primarily by HPV followed by Pap triage
Looking Towards the Future

- Ultimately a combination of vaccine in younger women and screening for carcinogenic HPV in older women may revolutionize cervical cancer prevention.

*See Schiffman, M, Castle, PE. The Promise of Cervical Cancer Prevention. NEJM 353:20, 2101-2104, 2005*