Goal of cervical cancer prevention

Cervical cancers develop from precursor lesions (CIN 3)
Average of 10 years for a high-grade lesion to progress to invasive cancer

CIN 3 Microinvasion Invasion

Widespread introduction of the Pap begins

1949 1996 2000’s

Conventional Pap smear LBC HPV testing Vaccine

Cervical cancer prevention: Where have we been and where are we going?

Goal of cervical cancer screening

- Prevention of morbidity and mortality from cancer.
- Prevention works via identification and destruction of cancer precursors.
  - Finding CIN
  - Finding abnormal Pap’s
  - Finding HPV

Limits to screening

- Attempting to prevent all cervical cancers is unrealistic and harmful.
  - Cancers in youngest women may not be detectable by screening
  - To achieve total prevention would require high sensitivity screen (e.g. HPV) at frequent intervals (< 1 year) with treatment of equivocal or mostly transient abnormalities
- Harms outweigh benefits.
Potential harms from screening

- Stigma, disrupted relationships, anxiety and distress
- Lost time
- Expense of investigation for lesions destined to regress
- Pain, injury from colposcopy and treatment
- Adverse pregnancy outcomes

Carcinogenic risk

Persistent positivity with oncogenic HPV types uncommon but required for progression. HPV 16 uniquely carcinogenic

Risks of human papillomavirus (HPV) persistence and progression.

Who was involved in framing screening guidelines?

Cervical cancer screening

Special considerations of women who fall outside of the guidelines
2012 Consensus Guidelines
Who should be screened outside of the screening guidelines?

Recommendations NOT intended for women with HIV, immunocompromised state, or in utero DES exposure.

4. NCCN Cervical Cancer Screening Guideline v. 2-2012. www.NCCN.org

2012 Consensus Guidelines
Women with prior HPV Vaccination

Recommended screening practices should not change on the basis of HPV vaccination.

4. NCCN Cervical Cancer Screening Guideline v. 2-2012. www.NCCN.org

Not addressed

20 year old G1P1 presents for a Rx for OCPs. She has had annual Pap's (all normal) since her pregnancy at age 16. She has had 7 partners since age 15 and a new partner for 3 months. What would you advise her about cervical cancer screening?

1. No Pap test now but at age 21.
2. Pap test now and annually because of multiple partners.
3. HPV testing now.
4. Pap test and HPV testing at age 21.

2012 Consensus Guidelines
When to begin screening

Women younger than 21 Years: No screening.

Concepts of HPV infection by age

HPV infections in adolescents and young women.
Benign and reversible disease.

HPV infections in adult women.
Risk of persistent infection and advanced CIN >> Invasive CA.

Rates of Cervical Cancer 2002-2006 SEER Data

<table>
<thead>
<tr>
<th>Age</th>
<th>Rate/100,000</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 10-14</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Age 15-19</td>
<td>0.1</td>
<td>0</td>
</tr>
<tr>
<td>Age 20-24</td>
<td>1.6</td>
<td>0.1</td>
</tr>
<tr>
<td>Age 25-29</td>
<td>5.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Age 30-34</td>
<td>11.0</td>
<td>1.4</td>
</tr>
<tr>
<td>Age 35-39</td>
<td>13.4</td>
<td>2.3</td>
</tr>
<tr>
<td>Age 40-44</td>
<td>15.3</td>
<td>3.4</td>
</tr>
<tr>
<td>Age 45-49</td>
<td>14.3</td>
<td>4.1</td>
</tr>
</tbody>
</table>

http://seer.cancer.gov
The incidence of cervical cancer has not changed in adolescents in the UK over the last 4 decades

**Despite increases in screening**


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**Risk in young women (age 21-24), not exactly adolescents**

- The risk of cervical cancer is 10-fold higher than risk in adolescents (1.4/100,000).
  - **High enough to justify screening.**
  - ~ 55,000 Pap’s must be obtained for every cervical cancer diagnosed.
  - **Low enough to allow observation** for minor cytologic abnormalities.

---

26 year old G3P3 had a Pap 4 years ago while pregnant. She is recently divorced and dating multiple men. Smokes 1ppd. Recent chlamydia. What cervical cancer screening is recommended now?

1. Pap only.
2. Pap and HPV testing (cotesting).
3. HPV only.
4. No screening now.

---

**2012 Consensus Guidelines: Screening Frequency**

**Age 21-29.** Testing with cytology (Pap) alone every 3 years.

- Co-testing should NOT be performed for women under age 30.
- Reflex HPV testing for ASCUS only.

---

**Determining screening intervals**

- USPSTF determined benefits and harms of screening at different starting ages and intervals.
  - **Screening every 3 yrs. with Pap’s starting at age 21 confers similar # of life-years as annual screening.**
  - **Screening beginning at age 21 at an interval of 3 years = most acceptable balance of benefits/harms (AHRQ 2011)**

---

What is the rationale for combined screening with HPV testing and Pap (co-testing) in women ≥ 30 years?
Which one of the following tests provides greater reassurance against CIN 3+ over an extended time?

1. Pap smear
2. HPV testing.

The Portland Kaiser Study
- 20,810 women followed for up to 122 months
- Over 45 mo, incidence of CIN 3+ = 4.54% if HPV+ or Pap > ASC-US. If both negative, incidence = 0.16%

Efficacy to predict CIN3+ within 45 mo.

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pap + HPV</td>
<td>68.4%</td>
<td>4.54</td>
<td>99.64</td>
</tr>
<tr>
<td>Pap alone</td>
<td>48.4%</td>
<td>9.63</td>
<td>99.47</td>
</tr>
<tr>
<td>HPV</td>
<td>75.4%</td>
<td>4.40</td>
<td>99.76</td>
</tr>
</tbody>
</table>

Sherman et al. JNCI 2003;95:46-52

Combining HPV and Pap Testing


Pap test and HPV testing

- HPV DNA detection has a 20-45% greater one time test sensitivity for CIN 3+ than cytology-based methods.
- CIN 2+ found by HPV testing and missed by cytology is clinically important.


Finding oncogenic HPV types does not provide a diagnosis of CIN 3 or cancer

It identifies a group of women in whom CIN 3+ is more likely...
Challenges of implementing HPV testing

- 66% of clinicians co-test at a frequency < q 3 years despite lack of benefit.
- Both low and high-risk HPV ordered despite the lack of benefit of low risk testing. (low risk HPV tests have no place in cervical cancer screening)
- Co-testing instead of Pap for women < age 30 (transient HPV does not warrant cotesting)

Lee et al. Obstet Gynecol 2011;118:4-13
Castle et al. Obstet Gynecol 2010;116:76-84

Kaiser Permanente Northern California data

- Risk analysis of 1.4 M women from Kaiser
  - 2003: shifted to co-testing; annual Pap's continued to be available.
  - > 1 M women age 30+ with cotesting.
    - 440 cancers
    - 3231 CIN 3+
    - 7581 CIN 2+
  - 400 K women age < 30 with cytology and HPV triage of ASCUS.
    - 26 cancers
    - 1231 CIN 3+
    - 4193 CIN 2+

KPNC conclusions

- 5 year risk of CIN 3+ following a negative co-test was comparable to a 3-year risk of CIN 3+ following a negative Pap.
  - Assesses cancer risk when high even when CIN 2+ risk is low.

What are immediate and future (5y) risks after x?

2013 ASCCP mgt guidelines

More use of cotesting to reduce follow-up visits

Management of Women > Age 35, who are Cytology Negative, but HPV Positive

- Repeat co-testing @ 1 year
- HPV DNA Typing Negative
- HPV 16 or 18 Positive
- HPV 16 and 18 Negative
- Repeat co-testing @ 1 year
- Repeat co-testing @ 7 years
- Colposcopy
- Biopsy per ASCCP guidelines

2013 ASCCP mgmt guidelines

More use of cotesting to reduce follow-up visits

Kaiser Study
N=331,818 women > 30 years in prospective co-testing study
35 year old G1P1 presents after routine co-testing showing a negative Pap test and positive HPV testing. She was previously screened with cytology only but has not had screening in 5 years. She’s had multiple sexual partners in the past year but before was monogamous for 15 years. What is the next step?

1. Routine screening in 5 years.
2. Immediate colposcopy.
3. Repeat HPV testing in one year.
4. Repeat both cytology and HPV testing (cotesting) in one year.

Proportion of Co-Test Results in 331,061 Kaiser women ≥ 30 years

<table>
<thead>
<tr>
<th>Result</th>
<th>Proportion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Both -</td>
<td>92.5%</td>
</tr>
<tr>
<td>Pap -</td>
<td>2.4%</td>
</tr>
<tr>
<td>HPV +</td>
<td>3.7%</td>
</tr>
<tr>
<td>Both +</td>
<td>1.4%</td>
</tr>
</tbody>
</table>

Discordant

2013 ASCCP consensus guidelines
Women > age 30, Pap -, HPV +

33 year old G2P2 presents for her Pap. No history of abnormal Paps. Last Pap 3 years ago. Monogamous. What is the preferred cervical cancer screening?

1. Pap and if negative, Pap every 3 years.
2. Co-testing and if both negative, cotesting every 5 yrs.
3. No cervical cancer screening is needed today.

2012 Consensus Guidelines: Screening Frequency

Age 30-65: Testing with cytology alone every 3 years or co-testing with cytology and testing for high-risk HPV types every 5 years.

- Co-testing “preferred” and cytology “acceptable” by all but USPSTF.
- USPSTF says either acceptable.

You are considering stopping cervical cancer screening in a 65 year old woman who has never had an abnormal Pap. She has not had co-testing but had 2 Pap’s in the past 10 years with the most recent one 2 years ago. Is her screening “adequate” enough to stop screening?

1. Yes
2. No
Adequate screening: ACOG, ASCCP, ACS*

*USPSTF does not define adequate screening

Adequate negative prior screening is defined as:
- 3 consecutive negative cytology results
- 2 consecutive negative co-tests
- done within the 10 years before stopping screening with the most recent test within 5 years.

Women older than 65 Years:
After adequate negative prior screening results.

2012 Consensus Guidelines: When to stop screening

Women older than 65 Years:
Screening should not be resumed for any reason, even if a woman reports having a new sexual partner.

71 year old woman’s husband died 5 years ago. She has no hx abnormal Pap’s and her last Pap was at age 66. New sexual partner. What would you advise her about cervical cancer screening?

1. Pap test only now.
2. Pap and HPV testing now.
3. Pap test 3 years after resuming sexual activity.
4. No further Pap test is necessary.

55 year old postmenopausal woman had a LEEP 2 years ago for CIN 3. She recently had a TAH for fibroids. What would you advise her about vaginal cancer screening?

1. She does not need further Pap tests.
2. She should have Pap tests until age 65 and then discontinue.
3. She should continue Pap tests for 20 years after her LEEP.

High grade vaginal intraepithelial neoplasia (VaIN 3) after TAH for CIN 3 in a 55 year old woman
No screening is necessary. Applies to women without a cervix and without a history of CIN2, CIN3, AIS, or cancer in the past 20 years. Evidence of adequate negative prior screening is not required (all but USPSTF). Screening should not be resumed for any reason, including if a woman reports having a new sexual partner.

2012 Consensus Guidelines: Women with prior hysterectomy

<table>
<thead>
<tr>
<th>Percentage of women who had a Pap test within 3 years by hysterectomy status and age group</th>
</tr>
</thead>
</table>

4. NCCN Cervical Cancer Screening Guideline v. 2-2012. www.NCCN.org

Thanks!
See you soon for management guidelines of abnormal Pap’s