Cervical Cancer Prevention throughout the Lifespan

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Objectives

Understand how HPV infections cause cancer

Understand how HPV vaccination prevents cancer

Understand the latest guidelines for cervical cancer screening and management of abnormal results
Cervical cancer prevention throughout the lifespan

• Ages 9-20
  – HPV vaccination

• Ages 21-26
  – Screening + catch-up vaccination

• Ages 27-65
  – Screening
HPV infection occurs in young adulthood, cancers develop 10-30 years later

Genital HPV infection 79 million

Cervical Pre-cancer 330,000

Cervical Cancer 12,000

Source: Schiffman M et al., 2013
Most HPV infections become undetectable in 1-3 years; those that persist cause precancer (CIN3+) over time.
Most HPV infections become undetectable in 1-3 years.

Precancer and cancer increase markedly when infections persist for 5 years or more.

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**Diagram Description:**
- **X-axis:** Years since infection with carcinogenic HPV
- **Y-axis:** Percentage of carcinogenic HPV infections
- **Graph 1:**
  - **Persistence**
  - **Clearance**
  - **CIN3**
- **Graph 2:**
  - **Invasion**
  - **CIN3 persistence or regression**
  - **X-axis:** Years since diagnosis with CIN3
  - **Y-axis:** Percentage of CIN3
HPV cancer prevention has two phases

1) Vaccinating adolescents to prevent infections that can lead to cancer
2) Screening adults to detect and treat precancer before cancer develops
HPV vaccination: Current ACIP/AAP Recommendations

- HPV vaccine now *recommended* for all adolescents ages 9 through age 26
- On-time vaccination is ages 9–12
- Catch-up vaccination ages 13-26

- *Individual decision making* for individuals age 27-45 (not routinely recommended due to low benefit)
HPV Vaccination of KidsEliminates HPV Infection and the Downstream Consequences

Genital HPV infection 79 million

Cervical Pre-cancer 330,000

Cervical Cancer 12,000

Source: Schiffman M et al., 2013
Near elimination of cervical cancer before age 30

- Girls vaccinated before age 17 were 88% less likely to develop cervical cancer
- Cervical cancer screening began at age 23, so this reduction was in addition to screening

Now we have a total of 3 studies showing the same results:
- Sweden (https://pubmed.ncbi.nlm.nih.gov/32997908/)
Is the HPV vaccine safe?

Yes!
What is the best way to prevent cervical cancer in adults?

- 13,800 cases annually (2020)
- 4,290 deaths annually (2020)


Cervical cancer incidence higher in rural counties and higher among Black and Hispanic women
Screening and treatment of precancers prevents cancer

Genital HPV infection 79 million

HPV Infection

Cervical Pre-cancer 330,000

HSIL

Cervical Cancer 14,000

Source: Schiffman M et al., 2013
Fundamental concept #1

- The longer an HPV infection has been present, the higher the risk of pre-cancer and cancer
  - *Time matters*
  - *Type matters (HPV 16 most dangerous)*
  - *Other patient factors less important if you know about HPV*
HPV testing detects more precancer (CIN3+) than Pap testing

- Pap testing is less sensitive than HPV testing
  - Detects 50-70% of CIN3+ vs >90%

- Cytology alone does not confer long-term protection against CIN3+ following a negative test

Dillner, BMJ 2008
Current screening recommendations

- **Age 21-24**
  - Pap testing only every 3 years*
  - HPV vaccination if not already vaccinated**
- **Age 25-29**
  - Pap testing every 3 years* or HPV testing every 5 years***
- **Age 30-65**
  - HPV testing every 5 years*
  - Pap/HPV cotesting every 5 years*
  - Pap testing every 3 years*
- **Age >65**
  - Discontinue screening if no prior abnormalities and 10 years of documented normal screening*,***

*USPSTF 2018; ACOG, ASCCP, SGO 2021; ACIP 2006, 2019 **; note ACS endorses 5-yr HPV testing
Who is eligible for a 5-year screening interval?

- Abnormal uterine/vaginal bleeding? [YES → Pap test part of diagnostic workup even if not due for screening]
- Hysterectomy that removed the cervix? [YES → Stop screening unless history of high grade precancer or cancer]
- HIV+ or immunosuppressed? [YES → Screen per immunosuppression guidelines]
- Abnormal test results within 10 years or treatment for precancer within the past 25 years? [YES → Follow ASCCP Risk-Based Management Consensus Guidelines]

QUALIFIES FOR ROUTINE SCREENING
Goals are to increase accuracy and reduce complexity for providers and patients

The 2019 guidelines are designed to be enduring, unlike prior versions which required major updates every 5-10 years to adjust for new technologies and emerging evidence.

Fundamental concept #2: Management is based on risk, not results

• Recommendations of colposcopy, treatment, or surveillance will be based on a patient’s risk of CIN3+ determined by a combination of current results and past history (including unknown history).

• The same current test results may yield different management recommendations depending on the history of recent past test results.
Past history influences current risk

**CIN3+ immediate risk (%) for current HPV-positive ASC-US result**

- Cotest negative: 2.0%
- Unknown: 4.5%
- HPV+ NILM: 5.4%
- CIN2+ treatment: 10.2%
Personalized recommendations improve management

- Expedited diagnosis and treatment for *high-risk* patients

- Fewer invasive procedures on *low-risk* patients

- *Risk stratification allows visit prioritization when addressing COVID-related practice changes*
Prioritizing Patients to Minimize Cancer Risk

DO NOT SCREEN

After age 65 if fulfills all of these exit criteria:

- Not immunosuppressed/HIV+
- No history of cervical cancer
- No cervical precancer in past 25 years
- No abnormal result in past 10 years
- At least 3 negative Paps or 2 negative HPV tests or co-tests in past 10 years

Otherwise keep screening until criteria are met

25% of cervical cancers are diagnosed in women >65
Most 64-66 year old women are *not* eligible to exit screening

<table>
<thead>
<tr>
<th></th>
<th>Privately insured cohort (all)</th>
<th>Privately insured cohort (10 years)</th>
<th>Safety net cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total population</td>
<td>590,901</td>
<td>108,641</td>
<td>1,544</td>
</tr>
<tr>
<td>Eligible to exit</td>
<td>22%</td>
<td>42%</td>
<td>34%</td>
</tr>
<tr>
<td>Ineligible due to lack of screening</td>
<td>65%</td>
<td>37%</td>
<td>57%</td>
</tr>
<tr>
<td>Ineligible due to high-risk condition</td>
<td>13%</td>
<td>22%</td>
<td>9%</td>
</tr>
</tbody>
</table>

Mills et al, Gyn Oncology, 2021
What about patients with abnormal results?
Paradigm Shift

Algorithm-based guidelines are like a map
Risk-based guidelines are like a GPS
Guiding principle: Equal management for equal risk

<table>
<thead>
<tr>
<th>HPV</th>
<th>Pap</th>
<th>N</th>
<th>%</th>
<th>Current risk of CIN3+ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pos</td>
<td>HSIL+</td>
<td>3980</td>
<td>0.3%</td>
<td>48.86</td>
</tr>
<tr>
<td>Pos</td>
<td>ASC-H</td>
<td>3766</td>
<td>0.2%</td>
<td>25.73</td>
</tr>
<tr>
<td>Neg</td>
<td>HSIL+</td>
<td>183</td>
<td>0.0%</td>
<td>25.21</td>
</tr>
<tr>
<td>Pos</td>
<td>ASC-US</td>
<td>30506</td>
<td>2.0%</td>
<td>4.45</td>
</tr>
<tr>
<td>Pos</td>
<td>LSIL</td>
<td>23659</td>
<td>1.5%</td>
<td>4.27</td>
</tr>
<tr>
<td>Pos</td>
<td>NILM</td>
<td>63541</td>
<td>4.1%</td>
<td>2.13</td>
</tr>
<tr>
<td>Neg</td>
<td>LSIL</td>
<td>3300</td>
<td>0.2%</td>
<td>1.05</td>
</tr>
<tr>
<td>Neg</td>
<td>ASC-US</td>
<td>25331</td>
<td>1.6%</td>
<td>0.04</td>
</tr>
<tr>
<td>Neg</td>
<td>NILM</td>
<td>1388153</td>
<td>89.8%</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Risk thresholds are based on prior guidelines for colposcopy and follow-up.

Risk Threshold Framework

Is Immediate CIN3+ Risk 4% or higher?

- Yes
  - Look at Immediate CIN3+ Risk for management
    - Expedited Treatment Preferred
      - 60-100% immediate CIN3+ risk
    - Expedited Treatment or Colposcopy Acceptable
      - 25-59% immediate CIN3+ risk
    - Colposcopy recommended
      - 4-24% immediate CIN3+ risk

- No
  - Look at 5-year CIN3+ Risk for management
    - Return in 1 year
      - ≥0.55% 5-year CIN3+ risk
    - Return in 3 years
      - ≥0.15% 5-year CIN3+ risk
    - Return in 5 years
      - <0.15% 5-year CIN3+ risk
Translating guidelines into management

Manage *high-risk* more aggressively

Manage *medium risk* the same

Manage *low-risk* less aggressively
Patients at very high risk should be referred for expedited treatment

- Specific combinations of test results are so high-risk that patients should proceed directly to a diagnostic excisional procedure (LEEP).
  - HPV 16+ HSIL
  - HPV-positive HSIL in patients who are underscreened (defined as no screening in more than 5 years)
Rationale for expedited treatment

- Reduces risk of missed diagnosis at colposcopy
- Allows simultaneous diagnosis and treatment
- Reduces loss to follow-up as requires fewer clinic visits
How do you explain this?

• Sample script for talking to patients:

• “The results of your screening tests indicate that you probably have precancer. They do not indicate cancer, which is excellent, but I recommend that we do a treatment procedure. This will both give us the information of a biopsy (making sure you don’t have cancer) and will also treat your precancer at the same time.”

• Provider should then explain LEEP procedure in detail and offer patient option of colposcopy with biopsy if they prefer.
Patients at medium risk should be referred for colposcopy

- Anyone who is HPV+ twice in a row
- Any HPV16 or HPV18 positive
  - even if pap results are normal
- Any high grade Pap result (ASC-H, AGC, HSIL)
  - even if HPV results are negative
- Low-grade pap results that are HPV positive (ASC-US or LSIL)
  - Unless preceded by a negative HPV screening test or co-test within 5 years or by a normal colposcopy within 1 year
Translating guidelines into management

Manage low-risk less aggressively

Manage medium risk the same

Manage high-risk more aggressively
Documented prior negative HPV lowers risk

<table>
<thead>
<tr>
<th>HPV</th>
<th>Pap</th>
<th>Immediate risk (%) after prior HPV neg</th>
<th>Immediate risk (%) no prior HPV test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pos</td>
<td>HSIL+</td>
<td>32.28</td>
<td>48.86</td>
</tr>
<tr>
<td>Pos</td>
<td>ASC-H</td>
<td>13.56</td>
<td>25.73</td>
</tr>
<tr>
<td>Neg</td>
<td>HSIL+</td>
<td>13.80</td>
<td>25.21</td>
</tr>
<tr>
<td>Pos</td>
<td>LSIL</td>
<td>2.10</td>
<td>4.27</td>
</tr>
<tr>
<td>Pos</td>
<td>ASC-US</td>
<td>2.03</td>
<td>4.45</td>
</tr>
<tr>
<td>Pos</td>
<td>NILM</td>
<td>0.74</td>
<td>2.13</td>
</tr>
<tr>
<td>Neg</td>
<td>LSIL</td>
<td>0.44</td>
<td>1.05</td>
</tr>
<tr>
<td>Neg</td>
<td>ASC-US</td>
<td>0.014</td>
<td>0.04</td>
</tr>
<tr>
<td>Neg</td>
<td>NILM</td>
<td>0.001</td>
<td>0.002</td>
</tr>
</tbody>
</table>

LSIL/ASCUS no longer meets colposcopy threshold

Patient case— how do you explain this?

• Sample script for talking to patients:

“The fact that you just tested negative for HPV means that this infection has not been active in your cervix for very long. The new positive test could mean a new infection, or it could mean that an old exposure that you had sometime in the past has become active again. The good news is that your risk of developing pre-cancer of the cervix is very low in either case, so we don’t need to do a biopsy this year. You need to come back next year for another test. If the test is still positive, then you will need a biopsy at that time.”
**Surveillance intervals**

<table>
<thead>
<tr>
<th>5-Year Return:</th>
<th>3-Year Return:</th>
<th>1-Year Return:</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIN3+ risks equivalent to general population with one negative HPV or cotest</td>
<td>CIN3+ risk equivalent to general population with negative Pap test</td>
<td>CIN3+ risks between colposcopy threshold and 3 year return threshold</td>
</tr>
</tbody>
</table>

1-year return means the patient is at high risk—these patients should be actively tracked.
Fundamental Concept #3: after an abnormal result, patients enter a surveillance period of close follow up

• All abnormalities require an initial period of intensive surveillance followed by a longer period of surveillance at 3 year intervals
The length of intensive surveillance depends on the abnormality

- Low-grade abnormalities:
  - HPV test or cotest at 1 year
  - Extend to 3 year intervals if negative
  - Continue for at least 10 years

- CIN2/3 after treatment
  - HPV test or cotest at 6 months, 18 months, 30 months
  - Extend to 3 year intervals if all tests negative
  - Repeat colposcopy for any HPV-positive result
After initial intensive surveillance, screening resumes at 3 year intervals using HPV testing or cotesting or annual intervals if using Pap alone.

- Surveillance should continue for at least 25 years after treatment for CIN2/3
  - Even if patient undergoes hysterectomy
  - Even if patient is over age 65
  - Screening may continue past age 65 if the patient is in good health
• ASCCP App

ASCCP Risk-Based Management Consensus Guidelines

The ASCCP Management Guidelines App & Web Application is Now Available

Streamline navigation of the ASCCP Risk Based Management Consensus Guidelines with the NEW ASCCP Management Guidelines App

- Evidence-based management guidelines
- Simple navigation
- Uncomplicated guidance
New resource containing USPSTF and ACS screening guidelines, ACIP HPV vaccine guidelines, and personalized tool with ASCCP guidelines for abnormal results: www.cervicalrisk.com

Cervical Cancer Risk Assessor

Welcome

This website provides information designed for patients and the general public to better understand cervical cancer screening and HPV vaccination.

Please choose one of the following options:

- Personalized Risk Assessment
- HPV and Pap Test Information
- HPV Vaccine Information

ABOUT US: The content for this website was developed by researchers at Boston University, with input from the National Cancer Institute, Centers for Disease Control and Prevention, and American Cancer Society. Software was engineered by Aiden Taghnia. This website aims to help people without advanced understanding of medicine or medical terminology understand changes in screening and management guidelines. We developed this website because there are currently few resources available to help patients in this area. This website does not provide medical advice. For a complete evaluation, please see your healthcare provider. This website will be updated in response to guidelines changes in collaboration with the National Cancer Institute. Most recent update was October 22, 2021.
With tremendous thanks to:

- NCI statistical team
- KPNC team
- ASCCP staff
- Working Group participants
- Steering committee members
- Consensus Voting Participants