Risk-based guidelines for management of abnormal cervical cancer screening test results: *raising the bar on prevention*

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HPV/Cervical Cancer Summit
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Disclosure of commercial interest

- No conflicts of interest to report

HPV infection and the downstream consequences

HPV-related cancers in women by age

Most HPV infections clear... those that persist cause CIN3+ over time... knowing HPV history can predict current and future risks

Screening detects CIN3 (“pre-cancer”)  ↓

Treating CIN3 prevents cancer  ↓

Goal of screening is to detect CIN3 and *prevent* cervical cancer
**Risk of cervical cancer with untreated CIN3 over 30 years**

**Untreated CIN3**: 30% (95% CI 22.7-42.3) chance of developing invasive cancer over the next 30 years

**Treated CIN3**: <1% (95% CI 0.3-1.9) chance of developing cancer

Based on data from the National Women’s Hospital, Auckland, New Zealand, where treatment of CIN3 was withheld from a substantial number of women between 1965 and 1974

MR McCredie et al, Lancet Oncol. 2008 May;9(5):425-34

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**Existing screening and management guidelines treat all women the same way**

*But past history predicts future risk*

Upcoming ASCCP guidelines for the management of abnormal results will incorporate history AND test result to determine the next step in a woman’s care

Schiffman et al., J.GTD, 2016

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**Examples of Risk Modifiers that predict CIN3+ risk**

**HPV vaccination** reduces risk of CIN2+

**HPV testing** predicts future risk better than cytology

- 331,818 women over 2003-2009
- Followed for 5 years for CIN3+
- Both HPV and cytology predicted risk on the date of screening
- HPV predicted 5-year risk of CIN3 and cancer

Multiple negative HPV tests predict very low cancer risk

Cancer risk fell from 9.2/100,000 after first negative HPV tests to 1.5/100,000 after 3rd consecutive negative HPV test.

New HPV infection confers lower CIN3+ risk

- 331,818 women over 2003-2009
- Risk of CIN3+ at 3 years
  - 5% with unknown prior HPV result
  - 3% with negative prior HPV result
- Prior negative HPV test reduced risk of CIN3+ with a new HPV+ result

Prior HPV+ or unknown history is higher risk

- 26,799 women with a current positive HPV+ test and no prior CIN2+
- Cumulative CIN3+ incidence rates over 4 years among women with current HPV+/Pap neg screen
  - Prior HPV positive: 4.36
  - Prior HPV negative: 1.32
  - Prior HPV unknown: 4.67
- Note prior HPV+ have the same risk as women with an unknown screening history

Long-term persistent HPV is especially high risk

- 8656 women age 20-29 underwent co-testing years 1 & 3
- Followed for 12 years for CIN3+
- Risk of CIN3+
  - 47% persistent HPV16+
  - 19% persistent HC2
  - HPV neg 2%
- HPV history is an important risk modifier

All women with persistent HPV develop CIN2+

195 women pap neg/HPV+ at start, 40 remained HPV+ for 7 years and all developed CIN2+

Treated CIN2+ has a high risk of recurrence within 5 years of treatment

- 8-16% risk after treated CIN3/AIS
- 5-10% risk after treated CIN2
- 0.08% risk after neg/neg co-test

- Thus history of CIN2/3 denotes 100-fold CIN2+ risk over negative co-testing, even after treatment

Elfgren, AJOG, 2017


Castle et al, Annals of Internal Medicine, 2018

Why revise ASCCP management guidelines to include risk data?

1. Detect and treat more precancer
2. Decrease testing and treatment that won’t prevent cancer and may cause reproductive harm
   
   
   Risk-based testing should allow better precancer detection in high-risk women, and fewer procedures in low-risk women

New ASCCP risk-based guidelines

- Patient’s current test results and past history
- Risk matrix is used to calculate her risk of CIN2/3
- Computer program generates risk score
- Recommends next step in management

Clinical trials

High quality observational studies

Medical record data

Clinical consensus

Risk matrix:

Calculating risk of CIN2+/CIN3+ for all meaningful combinations

Setting risk-action thresholds

Consortium, including ASCCP, CISNET, DCCPS, others

Clinical recommendations
Can be adjusted for methods in development

<table>
<thead>
<tr>
<th>Cytology-based</th>
<th>Molecular</th>
<th>Visual</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytology / Automation</td>
<td>HPV genotyping</td>
<td>VIA / Automation</td>
</tr>
<tr>
<td>Methylation</td>
<td>p16/Ki-67 / Automation</td>
<td>Imaging</td>
</tr>
</tbody>
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**Working groups**

- Treatment
- Colposcopy
- Surveillance
- Risk Modification
- New Technologies
- High value care
- Communication

**Projected timeline**

- Working groups review data and draft recommendations
  - Fall/Winter/Spring 2018
- Release of draft recommendations for public comment
  - Summer 2019
- Voting and final ratification of guidelines by consensus organizations
  - Fall 2019
- Public release of guidelines via app
  - Spring 2020

**Changing Gears:**

**Approved Expansion of HPV Vaccination to Age 45: What Does It Mean?**

Adapted from Webinar given 10/29 with Debbie Saslow, PhD | Senior Director, HPV-related and Women’s Cancers, American Cancer Society & Vice Chair, National HPV Vaccination Roundtable

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**HPV vaccination OF KIDS eliminates HPV acquisition, which eliminates downstream consequences of pre-cancer and cancer**

Schiffman M et al. CEBP 2013.

**Decrease in HPV infections in the U.S.**

*Pre-Vaccine Era, Early Vaccine Era and Later Vaccine Era*

Study also found vaccine type HPV decreased 89% for vaccinated girls, and 34% for unvaccinated girls: indicates herd immunity

So what about vaccination of adult women?

Effectiveness and cost-effectiveness
- 11 studies from 6 countries
- 2/3 of studies did not show effectiveness or cost-effectiveness for women over age 20

Timeline
- October 5th, 2018: FDA approved Gardasil 9 for men and women ages 27-45 years
  - Based on safety and efficacy in a clinical trial
- February 27-28, 2018: ACIP presentations on additional evidence and economic analysis, potential vote considering
  - Disease burden
  - Effectiveness (in a real world setting)
  - Cost-effectiveness

Burden of Disease
- Vaccinating through age 26
  - Estimated to prevent 25,000 HPV-related cancers annually
- Vaccinating through age 45
  - Estimated to prevent only 193 more cancers

Zero Cases of HPV-Related Cancers in Vaccinated Women

<table>
<thead>
<tr>
<th>Malignancy</th>
<th>HPV Vaccinated women (65,565 person-years)</th>
<th>Non-vaccinated women (124,245 person-years)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N  Rate (95% CI)</td>
<td>N  Rate (95% CI)</td>
</tr>
<tr>
<td>Cervix</td>
<td>0  -</td>
<td>8  6.4 (3.1, 13)</td>
</tr>
<tr>
<td>Vulva</td>
<td>0  -</td>
<td>1  0.8 (0.1, 5.7)</td>
</tr>
<tr>
<td>Oropharyngeal</td>
<td>0  -</td>
<td>1  0.8 (0.1, 5.7)</td>
</tr>
<tr>
<td>All HPV associated cancers</td>
<td>0  -</td>
<td>10 8.0 (4.3, 15)</td>
</tr>
</tbody>
</table>
People want to know

- Is it safe?
- Does it work?
- Will my insurance pay for it?

HPV vaccination is safe for all ages

- Common side effects are a sore arm, and occasionally short-term fever or headache, similar to other vaccines
- No serious side effects have been reported caused by the vaccine for kids or adults

Does it work?

- Will it work for me?
- Will it work for my child?

HPV vaccination works REALLY WELL for kids....
... But less well after age 18

Not much cervical pre-cancer was prevented by vaccination in 27-45 year old women

Who is most likely to benefit?

1) Kids
2) Adults whose HPV risk approximates those of 11-12 year olds
Should you vaccinate the whole family?

- Kids should all be vaccinated. Clear evidence of benefit. Vaccine is safe.
- Mom and dad can be vaccinated. Possible benefit by preventing HPV types they don’t have now but may be exposed to in the future. Vaccine is safe.

Will insurance cover vaccination for ages 27-45?

- It is probably NOT covered right now
- Coverage will depend on ACIP vote
- If Category B recommendation (individual decision-making), ACA mandates insurance coverage, though some issues can persist

In summary

- Vaccination of kids is **MOST IMPORTANT** and will prevent many cancers
  - Clear evidence of prevention of pre-cancers and cancers
- Vaccination of adults is an **INDIVIDUAL DECISION**
  - Limited evidence of benefit, but minimal risk
  - All adult women should continue cervical cancer screening

Other questions?