Understanding and Communicating Risks about HPV, SIL, and Cancer

Philip E. Castle, PhD, MPH
Professor, Epidemiology and Population Health, Albert Einstein College of Medicine
Executive Director, Global Coalition Against Cervical Cancer

castle.philip@gmail.com

April 6, 2017
Disclosures

• No financial relationships or conflict of interest to disclose
Courtesy of Bob Chapman (ACS)
First Principles

- Practically speaking, we cannot prevent all cervical cancer i.e., zero population risk is not really achievable.

- Any general screening must weigh the benefits against the harms, especially since the intervention is in the generally healthy population.

- Population risk can (and should) be used to as a guiding principle in clinical-decision making.
## Benefits vs. Harms

<table>
<thead>
<tr>
<th>Actual</th>
<th>Benefits</th>
<th>Harms</th>
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<tbody>
<tr>
<td>Cervical ≥CIN3 prevention</td>
<td></td>
<td>➢ Anxiety associated with a positive screening test&lt;br&gt;➢ Potential stigmatization from the diagnosis of a sexually transmitted infection&lt;br&gt;➢ Discomfort from additional diagnostic and treatment procedures&lt;br&gt;➢ Bleeding from treatment&lt;br&gt;➢ Increased risk of pregnancy complications such as preterm delivery due to treatment.</td>
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| Surrogate | Early Detection of CIN3 | Number of colposcopic referrals |
Harmonizing Management According To Risk

Castle et al., JLGTD, 2008
Reassurance following a Negative Test in 1 Million Women Undergoing Routine Screening

Gage et al., JNCI, 2015
Management of Women with Atypical Squamous Cells of Undetermined Significance (ASC-US) on Cytology*

- **Repeat Cytology**
  - @ 1 year
  - Acceptable

  - Negative
  - ≥ASC

    - Routine screening*

    - Colposcopy
      - Endocervical sampling preferred in women with no lesions, and those with inadequate colposcopy; it is acceptable for others

  - HPV Positive
    - (managed the same as women with LSIL)

    - HPV Negative

    - Repeat Cotesting @ 3 years

* Management options may vary if the woman is pregnant or ages 21-24.
+ Cytology at 3 year intervals

**Manage per ASCCP Guideline**
Management of Women with Low-grade Squamous Intraepithelial Lesions (LSIL)*‡

**LSIL with negative HPV test** among women ≥ 30 with cotesting

- Preferred
- Repeat Cotesting @ 1 year
- Cytology Negative and HPV Negative
- Repeat Cotesting @ 3 years

**LSIL with no HPV test**

- Acceptable
- Colposcopy
  - Non-pregnant and no lesion identified
  - Inadequate colposcopic examination
  - Adequate colposcopy and lesion identified

- Endocervical sampling “preferred”
  - Endocervical sampling “preferred”
  - Endocervical sampling “acceptable”

**LSIL with positive HPV test** among women ≥ 30 with cotesting

- CIN2,3
  - Manage per ASCCP Guideline

- No CIN2,3
  - Manage per ASCCP Guideline

* Management options may vary if the woman is pregnant or ages 21–24 years
‡ Manage women ages 25–29 as having LSIL with no HPV test

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“Risks” Are Simpler To Use Than Algorithms
Risks Following Negative Cotests

![Graph showing 5-Year Cumulative ≥CIN3 against Cotest Number for HPV+/LSIL and HPV-/ASC-US categories.](image)
Implicit Risk Thresholds Used in Current Pap-Only Screening

Katki et al, J Low Genit Tract Dis, 2013
Managing HPV+ and HPV-Equivocal Pap Results

Katki et al., J Low Genit Tract Dis, 2013
Managing HPV+ and HPV-Low-Grade Pap Results

Katki et al., J Low Genit Tract Dis, 2013
Managing HPV+ and HPV-High-Grade Pap Results

Katki et al., J Low Genit Tract Dis, 2013
Managing HPV+ and HPV-Pap-Negative Results

Katki et al., J Low Genit Tract Dis, 2013
1-Year Cumulative Detection of ≥CIN3

Castle et al., CEBP, 2016
Evaluation of p16 Triage in the Italian Screening Trial (NTCC)

- HPV-negative
- HPV-positive
- P16-negative
- P16-positive

Treatment

Colposcopy referral

Population risk

HPV-negative

HPV-positive

P16-negative

P16-positive (42% Referral)

Risk of precancer

Baseline

Year 3


Wentzensen, Lancet Oncol 2013
What Will Happen in a HPV16/18-Vaccinated Population?

Katki et al., J Low Genit Tract Dis, 2013
Final Comments

1. Perfection is the enemy of the good. No program will be perfect. The real question is what is the acceptable (residual) risk. Once defined, the appropriate screening interval will be self-evident.

2. Risk-based screening and management provides a framework to ensure that women receive appropriate care and incorporate secular changes in risk (e.g., HPV vaccination) and new tools (e.g., new biomarker assays).

3. We need to do a better job of translating risks into actionable steps...conveying guidelines and risks to the primary provider is not helpful and probably leads to poor compliance and communication to patients. Simple, clear, direct.

4. As Dr. Paul Han will discuss, population risks do not really apply to the individual, who either will or will not get the disease i.e., what do probabilities really mean to the individual?
A 42 year old woman with LSIL cytology and HPV16 has a n% risk of CIN3+, which is above the colposcopy referral threshold of m%. 

Patient: Doe, Jane
Age: 42
HPV: Pos
Genotype: 16
Cytology: LSIL
Vaccine: No
Last screen: positive

A

B

Absolute risk of precancer

Data entry

Recommendation

COLPOSCOPY REFERRAL
Clinical trials

High quality observational studies

Medical record data

Clinical consensus

<table>
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<tr>
<th>Risk strata</th>
<th>Immediate risk</th>
<th>1-year risk</th>
<th>2-year risk</th>
<th>3-year risk</th>
<th>4-year risk</th>
<th>5-year risk</th>
<th>6-year risk</th>
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<td>HPV and cytology</td>
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**Risk matrix:**
Calculating risk of CIN2+/CIN3+ for all meaningful combinations

Setting risk thresholds

Clinical recommendations