Epidemiology of HPV and Cervical Neoplasia

Implications for Optimal Vaccination and Screening

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TISSUE: Cervix

- Best understood site of HPV infection
- For all sites where HPV causes cancer:

  \[
  \text{HPV} + \\
  \text{Transformation Zone} = \\
  \text{Increased Risk of Carcinogenesis}
  \]
Transformation Zone – Histologically
EXPOSURE: HPV

* Evolutionary Tree (millions of years)

Burk, Virology 2005

α1, 8, 10, 13 Genital Warts

α2, 3, 4, 15 Commensal Infections

α5, 6, 7, 9, 11 Carcinoma & Precursors
DISEASE: Cervical Precancer and Cancer

Peak Ages:         15-25            25-35               45-50

Transient infection       HPV viral persistence

Normal cervix  Infection  HPV-infected cervix  Progression  Precancerous lesion  Invasion  Cancer
Clearance  Regression

Schiffman et al., Lancet, 2007
Epidemiologists Define Critical Steps From Normal to Cancer

Epidemiologists need reliable categories to define risks.
The First Step is HPV Infection

- Easily transmitted
- Each infection is independent
- A woman can have several, at the same or different times
- The peak incidence in a population is usually at young ages
Rapid Clearance is the Rule

Normal

Acute HPV
Persistence is Highly Associated with Risk of CIN3

- **Overt Persistence** is key risk factor for precancer
- HPV type very important
- Co-factors like smoking or parity less important
90% of New Carcinogenic HPV Infections Clear. Many but Not All that Remain Indicate Precancer
Kaiser Portland HPV Study (23,000 Women)
Cumulative Risk of Cancer, by HPV Type

Just one Test!
## Prospective Study of Cancer Death

<table>
<thead>
<tr>
<th></th>
<th>Cancer</th>
<th>Death</th>
</tr>
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<tbody>
<tr>
<td>HPV neg</td>
<td>8 / 24,000</td>
<td>0</td>
</tr>
<tr>
<td>HPV pos</td>
<td>87 / 2,800</td>
<td>12</td>
</tr>
</tbody>
</table>

8 year follow-up in randomized trial (130,000 women)

HPV arm of trial

Sankaranarayanan, NEJM, 2009
Clinical Viewpoint: Adapting to New Knowledge of HPV
Parts of “Old” Prevention Strategy

• Pap smear
• Colposcopic impression if Pap abnormal
• Biopsy if needed
• Treatment of CIN
• Follow-up
• Cytology, colposcopy, and biopsy have been great successes. We can now do even better.
HPV Testing: Major Randomized Trials

• All published in 2007-9
• Show screening with HPV tests is more sensitive for early detection of CIN3 than cytology
• HPV testing with or followed by cytology might be useful in some places, or other triage tests might be used
• In low-resource regions, screen-and-treat?
• New IARC Study in India by Sankaranarayanan et al. is a landmark study
Cervical Cancer Prevention Efforts Should Fit Age Patterns in Natural History

Schiffman and Castle, NEJM, 2006
If We Can Afford to Vaccinate…

Vaccinate before the peak of incidence, because the vaccines are preventive, and they do not work after infection occurs.
Screen *after* the peak of incidence, to improve specificity and positive predictive value.
Defining a New Clinical View of Cervical Carcinogenesis

There are many tests which, alone or combined, predict similar levels of risk.
“Risks” Are Simpler To Use Than Algorithms
Don’t Screen Too Often with HPV

(5-year cumulative incidence of CIN2+
following first HPV detection)

Good risk stratification with enrollment testing
Don’t Screen Too Often with HPV

(5-year cumulative incidence of CIN2+ following first HPV detection)

Infections found a year later predict lower risk of CIN2+

Year of First Positive HPV Test

<table>
<thead>
<tr>
<th></th>
<th>% Diagnosed with CIN2+</th>
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</thead>
<tbody>
<tr>
<td>Enrollment</td>
<td>16</td>
</tr>
<tr>
<td>First Follow-up</td>
<td>4</td>
</tr>
<tr>
<td>2nd Follow-up</td>
<td>0.6</td>
</tr>
<tr>
<td>Never Positive</td>
<td>0.03</td>
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</table>

N 1324 288 6626
Don’t Screen Too Often with HPV
(5-year cumulative incidence of CIN2+
following first HPV detection)

By year 2, any infections found are new and low-risk

Year of First Positive HPV Test

<table>
<thead>
<tr>
<th>Year of First Positive HPV Test</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrollment</td>
<td>1324</td>
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<tr>
<td>First Follow-up</td>
<td>288</td>
</tr>
<tr>
<td>2nd Follow-up</td>
<td>203</td>
</tr>
<tr>
<td>Never Positive</td>
<td>6626</td>
</tr>
</tbody>
</table>
Concluding Predictions

• Even better vaccines
• Decreased role for algorithms based on cytology, colposcopy and targeted biopsy
• More reliance on HPV-related tests and risk stratification to define management
• We need good epidemiology to inform new strategies