The Beginning Of the End of Cervical Cancer

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Maryland State Council on Cancer Control
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Persistent Human Papillomavirus (HPV) Infection -> Cervical cancer

Normal cervix

CIN3 (pre-cancer)

Invasive cancer

HPV
Estimated Annual Incidence of HPV Cervical Infection/Dysplasia

<table>
<thead>
<tr>
<th>Cervical Infection/Dysplasia</th>
<th>United States</th>
<th>Worldwide</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV infection without detectable cytologic abnormalities</td>
<td>10 million</td>
<td>300 million</td>
</tr>
<tr>
<td>Low-grade dysplasia</td>
<td>1 million</td>
<td>30 million</td>
</tr>
<tr>
<td>High-grade dysplasia</td>
<td>300,000</td>
<td>10 million</td>
</tr>
</tbody>
</table>

Virtually all cases of cervical cancer come from high-grade dysplasias.


U.S. rate = 4.64 / 100,000

Jon Kerner, PhD. Division of Cancer Control, NCI
Figure 3. Invasive Cervical Cancer Age-Specific Incidence Rates
Maryland and United States, 1994-1998

Age-specific rate per 100,000 population

<table>
<thead>
<tr>
<th>Age Group</th>
<th>MD</th>
<th>US</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-34</td>
<td>10.8</td>
<td>12.0</td>
</tr>
<tr>
<td>35-39</td>
<td>12.1</td>
<td>14.1</td>
</tr>
<tr>
<td>40-44</td>
<td>18.4</td>
<td>14.7</td>
</tr>
<tr>
<td>45-49</td>
<td>15.9</td>
<td>17.0</td>
</tr>
<tr>
<td>50-54</td>
<td>15.8</td>
<td>15.5</td>
</tr>
<tr>
<td>55-59</td>
<td>17.8</td>
<td>15.3</td>
</tr>
<tr>
<td>60-64</td>
<td>18.4</td>
<td>16.2</td>
</tr>
<tr>
<td>65-69</td>
<td>19.4</td>
<td>15.2</td>
</tr>
<tr>
<td>70-74</td>
<td>18.0</td>
<td>13.6</td>
</tr>
<tr>
<td>75-79</td>
<td>21.4</td>
<td>15.2</td>
</tr>
<tr>
<td>80-84</td>
<td>24.5</td>
<td>13.0</td>
</tr>
<tr>
<td>85+</td>
<td>22.0</td>
<td>13.8</td>
</tr>
</tbody>
</table>
Figure 4. Invasive Cervical Cancer Age-Specific Incidence by Race
Maryland and United States, 1994-1998

<table>
<thead>
<tr>
<th>Age Group</th>
<th>MD White</th>
<th>MD Black</th>
<th>US White</th>
<th>US Black</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-34</td>
<td>10.9</td>
<td>8.9</td>
<td>12.0</td>
<td>12.6</td>
</tr>
<tr>
<td>35-39</td>
<td>12.0</td>
<td>12.7</td>
<td>13.8</td>
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<td>55-59</td>
<td>15.4</td>
<td>21.9</td>
<td>12.4</td>
<td>28.1</td>
</tr>
</tbody>
</table>
JHH cervical cancer patients: 1984 - 2002
System Failures leading to Cervical Cancer Diagnosis

Patient does not get Appropriate therapy

Health care providers do not screen women at visits

Women do not come in for screening

Patient gets Cervical cancer

Colposcopy for Abnormal screen Not done

Source: P Pronovost
Persistent Human Papillomavirus (HPV) Infection -> Cervical cancer

Normal cervix -> HPV -> CIN3 (pre-cancer) -> Invasive cancer

Preventive vaccine

Treatment vaccines
# Prophylactic vs Therapeutic Vaccines

<table>
<thead>
<tr>
<th>Prophylactic</th>
<th>Therapeutic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhibit infection via induction of neutralizing antibody</td>
<td>Elimination of infected cells requires T cell responses - Ab ineffective</td>
</tr>
<tr>
<td>Require huge test populations</td>
<td>Relatively small test populations</td>
</tr>
<tr>
<td>Many years for validation</td>
<td>Viral clearance a rapid endpoint</td>
</tr>
<tr>
<td>Absolutely no tolerance for possible toxicity</td>
<td>Greater tolerance for possible toxicity</td>
</tr>
</tbody>
</table>
HPV prophylaxis: why pursue therapeutic vaccines?

- Prophylactic vaccines to prevent HPV infection are available within years.
  - Vaccines are effective only if immunization programs reach people before they are infected.
  - The prophylactic HPV vaccines are $120 a shot, you need three, over a six-month period, and you need an office visit for each shot. The barriers to getting vaccinated are the same as the barriers to getting screened.
  - The burden of HPV infection is massive.
- Cultural barriers exist to vaccination for a sexually transmitted infection
- It provides an opportunity to determine how to prevent cancer in patients with precancerous lesions.
Center for cervical disease at Hopkins

Established patient referrals and cohort retention: >1800 visits annually

Clinical trials infrastructure
- Clinical care team
- Research nursing
- Data management
- Study coordinator
- Research pharmacy
- Data safety/monitoring
- Regulatory staff
- HPV typing core lab
- Tissue banking

ENDPOINTS:
Histology, viral load, Immunologic monitoring*

Evaluation of immunotherapies in HPV disease
Johns Hopkins Center for Cervical Disease

Patient care/outreach

Teaching

Research
Premalignant HPV disease: low grade dysplasia

CIN 1
Low grade
Preinvasive
HPV DNA is episomal

benign

Host genome

CIN 1
Low grade
Preinvasive
HPV DNA is episomal
Premalignant HPV disease

CIN 1
Low grade
Preinvasive
HPV DNA is episomal

benign

CIN 2/3
High grade
Preinvasive
HPV DNA has integrated into host genome

malignant

Host genome

Host genome
CIN2/3 cohort clinical trials

Phase I/II vaccination trial: pNGVL4a-Sig/E7(detox)/HSP70

**v1**
- T = 4 wks

**v2**
- T = 6 wks
  - Interval colposcopy

**v3**
- T = 8 wks
  - Cone resection

**T = 15 wks**
- Postop check

**T = 19 wks**

Observational cohort study
Spontaneous regression over 15 weeks: precancerous lesions

Week 0

Week 15
Spontaneous regression of CIN2/3 over a 15-week observational window
HPV vaccines at JHH

- Combination strategies
- Needle-free delivery
The epidermis cannot be accessed with needle and syringe.

PowderMed device is designed to deliver to the epidermis.
GOG-JHU Cervical Cancer SPORE:

- GOG-SPORE collaboration to take advantage of unique clinical and scientific resources, and established, longstanding working relationships within GOG
  - Facilitate translation of promising therapeutic strategies: bench to bedside
  - Facilitate reverse translation of clinical findings: bedside to bench

GOG
- Cervix committee
- Committee on Experimental Medicine
  - Vaccine subgroup
- Cancer Prevention and Control Committee
- Pathology Committee

JHU Cervical Cancer SPORE
- Project 5: Immunotherapies in women with HPV16+ HGSIL
- Project 6: Immunotherapies in women with operable Stage IB1 Cervical Cancer
Vaccination strategies

Prophylactic vaccination

(age 12)
Vaccination strategies

(Prophylactic vaccination (age 12))

(Boost (age 25))
Vaccination strategies

(age 12)
Prophylactic vaccination

(age 25)
Prophylactic vaccination (boost)

screening

Prophylactic vaccination
Vaccination strategies

(age 12)
Prophylactic vaccination

(age 25)
(booster)
Prophylactic vaccination

screening

+HPV --> therapeutic vaccine
Lesion --> therapeutic vaccine
Johns Hopkins Center for Cervical Disease