Fast facts: cervical cancer

- Cervical cancer is preventable
- Cervical cancer is the second leading cancer killer of women worldwide
- Cervical cancer happens in the setting of a common viral infection
- Cervical disease is more common in women of lower socioeconomic means
- Cigarette smoking triples the risk of cervical disease
Persistent HPV infection
Cervical cancer

HPV16
E6 and E7

Additional
“hits”

Normal cervix  CIN3  Invasive cancer

Immortalized cells  Transformed cells
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

U.S. rate = 4.64 / 100,000

Jon Kerner, PhD. Division of Cancer Control, NCI

Legend
- Area with statistically significantly higher rate than U.S.
- Area with rate comparable to U.S. rate
- Area with statistically significantly lower rate than U.S.

Rates are age-adjusted to the 1970 U.S. standard population and are per 100,000 population.

U.S. Cervical Cancer Mortality Rate, 1994-1998: 2.7 per 100,000

Maryland Division of Health Statistics, 1994-1998

Source: Maryland Cancer Plan Web Site
Johns Hopkins Center for Cervical Disease

Patient care/outreach

Teaching

Research
Objectives: Maryland Cancer Plan

6.1: Conduct a follow-back study to determine factors that contribute to women developing and/or dying from invasive cervical cancer.
- different screening strategies
- different treatment algorithms
Retrospective Cohort Review of JHH and JHBMC patients with Squamous Cervical Cancer between 1984-2002

Women with Diagnosis
Squamous Cell
Carcinoma
Of Cervix

Socio-Demographics?
Medical, Gyn, and Sexual history?
Barriers to Care / Barriers to Access?

Who are they?
What happened?
Why?
Squamous cancer of the cervix, JHH/JHB, 1984-2002

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian</td>
<td>79%</td>
</tr>
<tr>
<td>African American</td>
<td>19%</td>
</tr>
<tr>
<td>Asian</td>
<td>1%</td>
</tr>
<tr>
<td>Other</td>
<td>1%</td>
</tr>
<tr>
<td>Mean age</td>
<td>45 (24-87)</td>
</tr>
</tbody>
</table>
Age distribution of cervical cancer cohort
JHH cervical cancer patients: 1984 - 2002
## Cohort Characteristics

| Exposure to Health Care system in the year prior to diagnosis | • OB/Gyn Office (65%)  
|                                                          | • Emergency Department (22%)  
|                                                          | • Primary Care Provider (36%) |
| Medical Co-Morbidities | • None reported (43%)  
|                                                          | • 1 or more (57%)  
|                                                          |  - HTN (23%)  
|                                                          |  - Respiratory dz (17%)  
|                                                          |  - DM (9%)  
|                                                          |  - Psychiatric (8%)  |
### Cohort Characteristics

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insurance</td>
<td>• Private Insurance (45%)</td>
</tr>
<tr>
<td></td>
<td>• Government Aid (29%)</td>
</tr>
<tr>
<td></td>
<td>• None (12%)</td>
</tr>
<tr>
<td>Telephone</td>
<td>• Yes (97%)</td>
</tr>
<tr>
<td>Employment</td>
<td>• Yes (54%)</td>
</tr>
<tr>
<td>Marital Status</td>
<td>• Married (52%)</td>
</tr>
<tr>
<td></td>
<td>• Single/Widowed (34%)</td>
</tr>
</tbody>
</table>
## Cohort Characteristics

<table>
<thead>
<tr>
<th>Category</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transportation</td>
<td>• Self (55%)</td>
</tr>
<tr>
<td></td>
<td>• Public, arranged (4%)</td>
</tr>
<tr>
<td></td>
<td>• Private, arranged (21%)</td>
</tr>
<tr>
<td></td>
<td>• Unknown (20%)</td>
</tr>
<tr>
<td>Education</td>
<td>• Not Completed HS (12%)</td>
</tr>
<tr>
<td></td>
<td>• Completed HS (36%)</td>
</tr>
<tr>
<td></td>
<td>• Unknown (52%)</td>
</tr>
<tr>
<td>Caregiver</td>
<td>• Yes (59%)</td>
</tr>
<tr>
<td></td>
<td>• No (41%)</td>
</tr>
</tbody>
</table>
Cohort Characteristics

<table>
<thead>
<tr>
<th>Recent Hospitalization</th>
<th>Yes  (25%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No (75%)</td>
</tr>
</tbody>
</table>
Cohort Characteristics

<table>
<thead>
<tr>
<th>Recent Hospitalization</th>
<th>Yes (25%)</th>
<th>No (75%)</th>
</tr>
</thead>
</table>

Maryland legislation mandates that women admitted to hospitals be offered a Pap test.
Thinking out of the box: in-reach

- Hopkins hospital in-house screening program: 1999-2002 (n = 1,117)
- Compared with outpatient screens from all of our clinics (n= 111,933)
- Cervical cancer precursors were nearly 5-fold higher in the hospitalized patients than in our outpatient clinics
Outreach: Cervical cancer screening at the Hispanic Apostolate

- Abnormal rate is high (12.2%)
- Comparison: abnormal rate in JHH outpatient clinics is 7% (close to the national rate)
- Comparison: abnormal rate in in-reach screening program at Hopkins: is 15.5%
Making a difference, starting at home

- Identify increased-risk populations in our catchment area
- Extend continuity of care to CRF sites
- Make the best treatment options available to our patients
Johns Hopkins Center for Cervical Disease

Multidisciplinary effort involving clinicians, immunologists, pathologists, virologists, oncologists, nurses, epidemiologists, biostatisticians: expertise on many levels

Mission: to improve screening, triage, and treatment, and to develop and evaluate interventions to prevent HPV-associated cancers of the lower genital tract
Tumor progression
Cervical cancer

HPV16
E6 and E7 Additional “hits”

Normal cervix CIN3 Invasive cancer

Immortalized cells Transformed cells
HPV Genome

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
HPV Genome

CIN 1
Low grade
Preinvasive
HPV DNA is episomal

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

Prophylactic vaccines

benign

malignant

Host genome

E2

L2

L1

LCR

E6

E7

E1

E2
HPV Genome

CIN 1
Low grade
Preinvasive
HPV DNA is episomal

benign

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

malignant

HPV DNA is episomal

CIN 1
Low grade
Preinvasive

Therapeutic vaccines

ctl

CIN 2/3
High grade
Preinvasive

Host genome

Host genome
HPV vaccines: the beginning of the end of cervical cancer

- Koutsky, et al, NEJM 2002
  - 2392 women, HPV16-naïve
  - Prophylactic VLP vaccine
  - 100% efficacy at 7 months

- ICAAC 2004 42 months of follow up
  - Vaccine efficacy: 94%
HPV prophylaxis: why pursue therapeutic vaccines?

- Prophylactic vaccines will only be effective if everyone gets immunized.
- The herd burden of HPV infection is massive.
- Cultural barriers exist to vaccination for a sexually transmitted infection.
- Curing early disease would also help us to figure out what is a good immune response.
- Science/discovery do not transpire out of a social context. (cancer vaccines, transplant, autoimmune diseases)
Center for cervical disease at Hopkins

- Clinical trials infrastructure
- Validated readouts
- Established patient referrals and cohort retention
- Evaluation of immunotherapies in HPV disease
Phase I/II clinical trials: HPV 16 E7-targeted therapeutic vaccines

• Target population: healthy women with preinvasive HPV16-associated disease of the cervix
• Two parallel cohorts
  - HIV-negative
  - HIV-positive
CIN2/3 clinical trials

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

v1
T = 0

v2
T = 4 wks
Interval colposcopy

v3
T = 8 wks
Cone resection

T = 6 wks

T = 15 wks
Postop check

T = 19 wks

Observational cohort study
## CIN 2/3 cohort study

### Patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (in years)</td>
<td>30.0y (range 18-67y)</td>
</tr>
<tr>
<td>&lt; 25</td>
<td>25 (25%)</td>
</tr>
<tr>
<td>25-34</td>
<td>53 (53%)</td>
</tr>
<tr>
<td>&gt;35</td>
<td>22 (22%)</td>
</tr>
<tr>
<td>Average time to resection</td>
<td>123.8 d</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>26 (26%)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>White</td>
<td>67 (67%)</td>
</tr>
<tr>
<td>Asian</td>
<td>4 (4%)</td>
</tr>
<tr>
<td>Reported number of partners</td>
<td>8.1 (1-50)</td>
</tr>
<tr>
<td>Tobacco smoking</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>42 (42%)</td>
</tr>
<tr>
<td>Former</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Never</td>
<td>56 (56%)</td>
</tr>
<tr>
<td>Hormonal contraceptive use</td>
<td>52 (52%)</td>
</tr>
</tbody>
</table>
Spontaneous regression over 15 weeks: CIN2/3

Week 0

Week 15
Interaction between HLA class I and HPV: effect on disease behavior

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimated O.R.</th>
<th>95% C.I.</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Months</td>
<td>1.01</td>
<td>0.86-1.19</td>
<td>0.87</td>
</tr>
<tr>
<td>HPV16</td>
<td>0.20</td>
<td>0.06-0.73</td>
<td>0.01 *</td>
</tr>
<tr>
<td>HLA*A201</td>
<td>0.90</td>
<td>0.03-29.44</td>
<td>0.95</td>
</tr>
<tr>
<td>-HPV16*-~HLA*A201</td>
<td>32.12</td>
<td>0.97-&gt;999.999</td>
<td>0.05 *</td>
</tr>
</tbody>
</table>

Trimble et al, SPORE 2004
CIN2/3 clinical trials

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

T = 0  T = 6 wks  T = 15 wks  T = 19 wks

v1  v2  v3
T = 4 wks  T = 8 wks

Interval colposcopy  Cone resection  Postop check

Observational cohort study
GMP-Grade pNGVL4a-Sig/E7(detox)/HSP70 DNA Vaccine
HPV vaccines at JHH

- Combination strategies
- Needle-free delivery
- Continued outreach
“Never, ever, think outside the box.”
Vaccination strategies

Prophylactic vaccination

(age 12)
Vaccination strategies

(age 12)
Prophylactic vaccination

(age 25)
(booster)
Vaccination strategies

- Prophylactic vaccination (age 12)
- Prophylactic vaccination (age 25 boost)
- Screening
- Prophylactic vaccination
Vaccination strategies

(age 12)
Prophylactic vaccination

(age 25)
Prophylactic vaccination (boost)

screening

Prophylactic vaccination

+HPV --> therapeutic vaccine
Lesion --> therapeutic vaccine
Vaccination strategies

(age 12)
Chimeric vaccination (combination prophylactic and therapeutic)

(age 25)
(booster)
HPV vaccines: long-term goals

- Combine prophylactic and therapeutic approaches on a population basis
- Eliminate the need for cumbersome screening
Johns Hopkins Center for Cervical Disease