an evolving understanding of an ancient and established virus
Disclosures-1

• Merck
  – Speaker Panel for Gardasil

• Hologic
  – Speaker Panel for Cervista and Thin Prep
Disclosures-2

Gynecologic Oncologist

Parent

Vaccine Enthusiast
Objectives

• HPV
• Cervical cancer
• The Cervix
• Epidemiology
• Screening tests
• Breast Cancer
Public Health

Environmental Health

Statistics

Alcohol

Healthcare

Occupational Health and Safety

Birth Defects

Behavior

Indicators

Big Data

Training

Family

Risk

Epidemiology

Cervical Cancer

Policy

Economics

Lead

Air

Toxins

Health

Data

Vaccines

Environmental

Toxicology

Sanitation

Infectious Disease

Sanitation

Infectious Disease

Aging

Influenza

Hospital

Oral Health

Influenza

Education

Safeguards

Addiction

Safeguards

HIV

Reproduction

Restaurants

Environmental Hazards

Food Safety

Vital Statistics

Use

Meaningful

Violence

Health

Preparedness

Non-communicable disease

Leadership

Vital Statistics

Reproduction

Preparation

HIV

Food Safety

Vital Statistics
Public Health

• Under valued in the USA
  – Funding
  – PhD vs MPH

• Under recognized
  – Public awareness
  – MD awareness

• Really important
  – Flu
  – Gun safety
Mortality over the years

- Pneumonia
- TB
- GI infections
- Cardiac disease
- Cerebrovascular dz
- Nephropathies
- Accidents
- Cancer
- Senility

- Cardiac disease
- Cancer
- Pulmonary causes
- Cerebrovascular dz
- Accidents
Concept of Cancer

• Largely dependent upon knowledge of normal
• No concept of prodromal cancer
• Early diagnosis: desired, though treatment options limited
• Prevention: unclear
Screening Test

- Performed on asymptomatic people
- Common disease
- Plausible test
  - Cost, Access, Reliable
- Sufficient “lead time” to intervene
- Intervention that can prevent death or morbidity
- (Public Health concept)
SCREENING

- Public Health mechanism
- For the asymptomatic patient
- Cost to patient and society
- Balance benefit versus harm
- Examples
  - Lead in the water?
  - Blood pressure
  - STI screening (GYT)
Diagnostic Test

• A test performed on someone who is symptomatic and needs DIAGNOSIS

• Xray, blood, biopsy

• Pap smear can be diagnostic
  – Vaginal bleeding

• Mammogram can be diagnostic
  – Breast lump

• Colonoscopy can be diagnostic
  – Rectal bleeding
SCREENING TESTS

- xray
- pap smear
- mammogram
- colonoscopy
- PSA
- stool guaiac
- “get yourself tested” STI screening
- vision screening
- scoliosis screening
- TB screening
- mobile CT scans
- blood pressure
PAP SMEAR

• Age range
  – under 21
  – over 65

• Risk factors
  – HPV Negative
  – Sexual partners
  – iatrogenic immunosuppression
Enter the Pap Smear

• Georgios Papanikolaou (1883-1962)
• 1920s describing the normal vagina
• 1928 presented his findings
• 1943 published his findings
• 1965 ACS recommended screening
• 1999 reflex HPV testing
• 2009 co-testing HPV and cytology
• 2014 HPV primary testing
Major Advances in Cervical Cancer Screening


- **1941** Pap Smear
- **1970s** Research by Harald zur Hausen linking HPV to cervical cancer
- **1996** ThinPrep® Pap Test
- **1999** SurePath® Pap Test
- **1999** Hybrid Capture® 2 HPV Test
- **2003** ThinPrep® Imaging System
- **2006** Gardasil® HPV Vaccine
- **2006** ThinPrep® Receives Glandular Indication
- **2009** Cervista® HPV HR Test and Cervista® HPV 16/18 Genotyping Test
- **2009** Cervarix® HPV Vaccine
ThinPrep® Liquid-based Cytology: Mitigates Sampling Error and Improves Preservation

**Conventional Smear**
- Majority of cells discarded
- Nonrepresentative transfer of cells
- Clumping and overlapping of cells
- Obscuring material

**ThinPrep Pap Test**
- Virtually all of sample is collected
- Randomized, representative transfer of cells
- Even distribution of cells
- Minimizes obscuring material

Screening Has Dramatically Reduced Cervical Cancer Incidence

US Cervical Cancer Incidence*

US Cervical Cancer Mortality*

* Insufficient data available for time trend analysis for American Indians/Alaskan Natives.
** Incidence and mortality data not available before 1992.

Limitations of Cytology

• Epidemiology
  – changing face of the disease

• Anatomy
  – screens ectocervix reliably but not endocervix

• Labor Intensive
  – limitations on cyto-technologist work force

• Cost
Advantages of HPV Screening

- HPV testing is more sensitive than cytology
- HPV testing has a high negative predictive value
- HPV testing is automatable and reproducible
- For women 30 and older, a negative Pap and HPV test would allow for a patient to extend to a 3-year screening interval\(^2\)

2. J Clin Oncol May 2011 vol. 29 no. 15_suppl 1508
Changing Epidemiology
HPV ONCOGENESIS
HPV in Cancer: History

• 1935 Francis Peyton Rous
  – caused skin cancer in rabbit

• 1972 Stefania Jablonska
  – identified HPV 5 in skin cancer

• 1976 Harald zur Hausen
  – hypothesized HPV cause of cervical cancer

• 1983 HPV 16

• 1984 HPV 18

• 2008 Nobel Prize in Medicine
Peyton Rous and Rous Sarcoma Virus (RSV)
HPV EPIDEMIOLOGY
Could YOU have HPV?
YES... if you have...

- a cervix
- a vagina
- a penis
- tonsils
- a throat
- an anus
- ever had sex
HPV is Ubiquitous

• 85% have come in contact with it
• The majority “clear it”
• More common in smokers
• More transmissible female to male
• Resides in epithelial layer
  – Basal layer required for replication
• Conserved in mammals
  – Across time and geography
“My patient is not at risk”

- Wife of Korean WHO Chief
- 4J school teachers
- Librarians, nurses
- The girl next door
- Anesthesiologists
- Social workers
Human Papillomavirus (HPV) Is a Cause of Cervical Cancer

- Over 100 types identified
- 30–40 anogenital

  - 15–20 oncogenic types, including 16, 18, 31, 33, 35, 39, 45, 51, 52, 58
    - HPV 16 (54%) and HPV 18 (21%) account for the majority of cervical cancers worldwide
  - Nononcogenic types include: 6, 11, 40, 42, 43, 44, 54
    - HPV 6 and 11 account for 90% of external genital warts

HPV Facts: Most common STD in the U.S.

Approximately 20 million Americans are currently infected.¹

- Estimated incidence of new cases 6 million per year¹
- 80% sexually active adults in U.S. infected w/ at least one HPV type by age 50¹
- Peak prevalence during adolescence and young adulthood
  - Among sexually active 15-24 year olds:
    - 74% new infections occur in this age group²
    - ~9.2 million currently infected²

¹. Centers for Disease Control & Prevention, Rockville MD: CDC National Prevention Information Network; 2009
My patient is not at risk

- HPV is ubiquitous virus
- Risk assessment does not work
  - HIV
  - Hep B
  - HPV vaccination
I'M A VIRGIN
(But this is an old shirt)
HEY WEST
US Cervical Cancer Statistics

• Approximately 12,710 new cases/year\(^1\)
• Approximately 4,290 deaths/year\(^1\)
• Approximately 10 million cases of HPV infection without cytologic abnormalities\(^2\)
• Approximately 1 million cases CIN 1\(^2\)
• Approximately 300,000–700,000 cases of CIN2/3
• Direct cost of prevention and treatment of cervical cancer is $6 billion annually in the US

33,000 cancer cases annually
HPV in Laryngeal Cancers

![Bar chart showing the number of genotypes for different HPV types in females and males.](image-url)

PLoS One 2014 Dec 29, 9(12)
Internationally

- 530,000 cases of cervical cancer
  - 230,000 deaths
- 30,000 cases of anal cancer
  - more female than male
- oropharyngeal cancer
  - new area of tabulation
- >600,000 cancer cases
  - >300,000 deaths
Why Are HPV 16/18 Important?

> 75% of *Squamous Cancers in the United States Are Caused by HPV 16/18*

<table>
<thead>
<tr>
<th>HPV Types</th>
<th>Cumulative Prevalence</th>
<th>Incremental Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>16 alone</td>
<td>54.7%</td>
<td></td>
</tr>
<tr>
<td>16 + 18</td>
<td>76.4%</td>
<td></td>
</tr>
<tr>
<td>+ 35</td>
<td>83.7%</td>
<td></td>
</tr>
<tr>
<td>+ 31</td>
<td>87.6%</td>
<td></td>
</tr>
<tr>
<td>+ 33</td>
<td>91.0%</td>
<td></td>
</tr>
<tr>
<td>+ 45</td>
<td>93.6%</td>
<td></td>
</tr>
<tr>
<td>+ 52</td>
<td>94.2%</td>
<td></td>
</tr>
<tr>
<td>+ 58</td>
<td>94.4%</td>
<td></td>
</tr>
<tr>
<td>+ 59</td>
<td>94.5%</td>
<td></td>
</tr>
</tbody>
</table>

Proportion of Cancers Associated with HPV Types

Phylogenetic Tree Basis of Cervista® HPV HR Test Design

<table>
<thead>
<tr>
<th>HPV Group</th>
<th>HPV Types</th>
</tr>
</thead>
<tbody>
<tr>
<td>A5/A6</td>
<td>51, 56, 66</td>
</tr>
<tr>
<td>A7</td>
<td>18, 39, 45, 59, 68</td>
</tr>
<tr>
<td>A9</td>
<td>16, 31, 33, 35, 52, 58</td>
</tr>
</tbody>
</table>
How does HPV do it?

- interferes with the normal work of the cell
  - invades epithelium
  - evades “surveillance”
  - integrates into host genome
- E6
  - interrupts important work of p53
- E7
  - interrupts important work of RB
- Able to create immortal cell lines
  - HeLa cells: HPV 18
HPV enters the epithelium

- trauma of intercourse
  - micro-abrasions
  - coexisting infections
- “dry” intercourse
- anal intercourse
- areas of metaplasia/transition
- oropharyngeal trauma
Normal Cervix with Ectopy

Source: Seattle STD/HIV Prevention Training Center at the University of Washington
Chen E. Stevens
Progression from HPV infection to Cervical Cancer

- **HPV Clearance**
- **HR HPV Infection**
  - Within 12 months
  - **CIN 1/2**
  - **CIN 2/3**
  - **Cervical Cancer**
  - 1-5 years
  - Persistent Infection

Progression to cervical cancer may take up to decades

HR = High risk
CIN = Cervical intraepithelial neoplasia

HPV targets the squamous epithelium found beneath the foreskin of the penis and also the cervix. Infection of basal epithelial cells is necessary for HPV replication and it is thought that virus particles gain access to these cells through microabrasion or microwounding that exposes the basement membrane. The L1 capsid protein on the surface of the HPV virion interacts with α6β4 integrins that are upregulated on basal epithelial cells during wound repair. Interaction with α6β4 integrin promotes internalisation of virus. Circumcision may reduce the risk of HPV infection via the removal of target cells present in the squamous epithelium beneath the foreskin. Antibodies to the capsid proteins L1 and L2 of HPV may be important in blocking attachment of virus to receptors on basal epithelial cells during microwound healing.
HPV takes advantage of the differentiation pathway of keratinocytes that are destined to die naturally (anoikis). Since HPV is not cytolytic and does not cause viraemia, there is no inflammation and subsequent activation of the immune system. Infection of basal epithelial cells establishes a latent infection with low level replication of the viral episome and minimal viral protein expression. Following differentiation of the keratinocyte, early HPV genes are expressed and the viral episome is further amplified to higher copy numbers. Viral late protein expression and virus assembly occurs during terminal differentiation of the keratinocyte and viruses are shed from the outermost layer of epithelial cells.
The role of p53 protein is to respond to DNA damages and functions as a nuclear transcription factor that activates transcription of genes involved in arrest of the cell cycle and induction of DNA repair systems or the induction of apoptosis. Retinoblastoma protein (pRb) functions to inactivate the transcription factor E2F-DP that is required to initiate transcription of genes involved in DNA replication. These two proteins are essential to prevent cells with damaged DNA from dividing and are known as tumour suppressor proteins. In the absence of HPV E6 and E7, p53 and pRb function normally and reduce the risk of malignant cell transformation.
Integration of the HPV genome with a disrupted E2 gene into host chromosomal DNA is a necessary event that can lead to the development of carcinoma. The E2 gene encodes a transcription factor that regulates the transcription of HPV E6 and E7 oncoproteins. In the absence of E2, increased synthesis of E6 and E7 protein occurs. E6 binds to p53 in the cytosol and also recruits the E6AP ubiquitin ligase that ubiquitinates p53 and targets it for proteosomal degradation. Similarly, HPV E7 binds to pRb in the cytosol and recruits the cullin 2 ubiquitin ligase that ubiquitinates pRb and promotes proteosomal degradation. Loss of cellular p53 and pRb tumour suppressor proteins allows a cell with DNA damage to divide and thereby increases the risk of cancer development.
TRAINED MY DOG TO IMPERSONATE 6 POLITICAL SEX SCANDALS AT THE SAME TIME.
Papillomaviruses are absolutely species specific and tissue specific.
Why Are HPV 16/18 Important?

> 75% of Squamous Cancers in the United States Are Caused by HPV 16/18

Proportion of Cancers Associated with HPV Types

Risk Stratification with HPV Types 16 and 18 in Women ≥ 30 Years of Age with Negative Cytology

In women ≥ 30 years of age, 10-year cumulative incidence of ≥ CIN 3 was 20% and 18% for HPV 16 and 18, respectively

Papanicolau to zur Hausen
Cervical Cancer Prevention:
Get with the times...

“This dial phone has always worked for me...”

“My patients would never be able to understand a more modern test...”
FUTURE DIRECTIONS
Vaccines

• Gardasil 4 (Merck) FDA approved 2006
  – 6,11,16,18

• Cervarix (GSK) approved 2009
  – 16,18

• Gardasil 9 (Merck) FDA approved 2014
  – 6,11,16,18,31,33,45,52,58

• Vaccines are controversial
Vaccine Efficacy

- 99-100% immunogenicity
- 92-99% efficacy
- Decrease CIN3 17-33%
- Decrease colposcopy by 10%
- Decrease treatment by 25%
- Impeccable safety record
Vaccine Eligibility

• Gardasil 4 and Cervarix
  – Girls 9-26
  – Boys 9-26
  – Safety data exists for the “older woman”

• Gardasil 9
  – Girls 9-26
HPV adjunctive testing

• Primary testing
  – controversial
• Cotesting
  – here to stay
• Enhanced HPV testing
  – Aptima test (Hologic) tests for mRNA
• Testing intervals
  – 3 lifetime screening tests?
Oropharyngeal Cancers

- 20-40% are HPV positive
- HPV 16
- Better prognosis
- Decreased morbidity from scaled back treatment regimens
The Future

• Vaccines prevent cervical cancer
• Therapeutic “vaccines” eliminate any remaining HPV
• Cervical cancer goes the way of small pox – ? (and measles?)
Adjunctive Testing (Pap + HR HPV)
**ASCCP Algorithm for HPV Genotyping**

*For Resolution of Discordant Results in Reflex Testing Women ≥ 30 Years*

---

**Use of HPV Genotyping to Manage HPV HR\(^a\)-Positive, Cytology-Negative Women 30 Years and Older**

- **HR HPV Positive, Cytology Negative**
  - HPV 16/18 Positive: **Colposcopy**
  - HPV 16/18 Negative: **Repeat BOTH tests at 12 months**

- **Both Negative**
  - Routine Screening at 3 Years

- **Cytology Negative, HPV-Positive**
  - **Colposcopy**

- **Cytology Abnormal, Any HPV Result**
  - Manage per ASCCP Guidelines

---

ASCCP = American Society for Colposcopy and Cervical Pathology

\(^a\)Test that detects any of the 14 HR (oncogenic) types of HPV.
**1st Review**
- Imager scans every cell and cell cluster on the slide, measuring DNA content

**2nd Review**
- Cytotechnologist reviews 22 fields containing “objects of interest”
  - Full slide screened if any cells judged abnormal

Clinical benefits over manually reviewed ThinPrep® Pap Test$^1$:
- Increased sensitivity
- Increased specificity
- Reduced false-negative fraction

Imaging System Focuses Slide Review

120 Fields of View → 22 Fields of View

ThinPrep® Imaging System Is Statistically More Sensitive Than Manual Screening

- TIS more sensitive than manual screening for:
  - ASC-US
  - Higher-grade lesions with equivalent specificity for ASC-US
  - LSIL
- Glandular malignancies not included in original studies, but data now support

Cells Are Collected in Liquid for Laboratory Processing

- **Healthcare Provider Office**
  - Sample collected

- **Laboratory**
  - Representative sample
  - Even distribution of cells
  - Minimal obscuring material

Dispersion/Collection/Transfer
BREAST CANCER

- Annual exams
  - Clinical exams and mammograms

- Epidemiologic concerns
  - parity, HRT, breastfeeding

- Treatment concerns
  - Tamoxifen, aromatase inhibitors

- Genetic concerns
  - BRCA mutation status
BREAST CANCER EPIDEMIOLOGY

- Being female (100:1)
- Age (stats determined through age 90)
- Exposure to estrogen
  - Obesity
  - Alcohol
  - Breastfeeding
  - Pregnancy history
  - HRT
- Prior radiation
  - lymphoma
“whether it would be permissible to make the ladies old more quickly by removing their ovaries…”

Schinzing, 1889
SIXTY-EIGHTH ANNUAL MEETING
OF THE
BRITISH MEDICAL ASSOCIATION

Held at IPSWICH, July 31st, August 1st, 2nd, and 3rd, 1900.

PROCEEDINGS OF SECTIONS.

SECTION OF SURGERY.

Howard Marsh, F.R.C.S., President.

ON ÖÖPHORECTOMY IN CANCER OF THE BREAST.

By Stanley Boyd, M.B., F.R.C.S., Surgeon, Charing Cross Hospital.
Distant History

• Dr. George Beatson (Lancet, 1896)
  – Capitalized on experience of Scottish sheep farmers
  – Removed ovaries of a premenopausal patient with advanced breast cancer

• Dr. Stanley Boyd (Br Med Journal, 1900)
  – Reported on 46 patients
  – 37% response rate
Endocrinology Unveiled

• 1923 “estrus stimulating principle”
  – “estrus” from the Latin “frenzy”
• 1962 synthesis of radioactive estradiol
  – Allowed identification of target tissues
• 1966 estrogen receptor isolated
Estrogen Receptor

- Separated tumors for treatment purposes
- Allowed stratification of tumors for prognostic purposes
- 1974: Estrogen Receptor discussed at NCI
  - ER + tumors had 60% response rate
  - ER- tumors had 10% response rate
Endogenous Hormonal Manipulation

- Obesity
- Pregnancy
- Breastfeeding
- Terminations
- Hormonal Contraception
Obesity

• Single most modifiable risk factor associated with diagnosis and prognosis
  – Complex association with medical comorbidities, therapy dosing
  – Multiple measures of obesity
• Across age ranges
  – Post and pre menopausal
• Associated with increased aromatase