Pathology of the Cervix

Thomas C. Wright

Pathology of the Cervix

Topics to Consider

Burden of cervical cancer
Invasive Cervical Cancer

*Cervical cancer in world*

Second cause of cancer death in women
Leading cause in many developing countries
471,000 cases; 233,000 deaths - 2000
Incidence varies dramatically with availability of screening

Parkin DM (2001) Lancet Oncology

Cervical Cancer in U.S.

*Statistics for 2007*

11,150 cases - invasive cervical cancer
3,670 deaths from cervical cancer
1 out of 50 cancer-related deaths
0.4% of all female deaths

American Cancer Society - Facts and Figures 2007
Pathology of the Cervix

Topics to Consider

Burden of cervical cancer
Epidemiology of cervical cancer

Cervical Cancer

Risk Factors

Number of sexual partners
Age at first intercourse
Low socioeconomic status
Parity and age first pregnancy
Previous STD’s
Smoking and immunosuppression
Impact of Female Behavior - Cervical cancer incidence

Impact of Male Behavior - Cervical cancer incidence
Sexually Transmitted Agent

Sexually Transmitted Agent

Stratified Squamous Immature Metaplastic Columnar Epithelium

No Effect Precursors & Cancer Usually No Effect

Risk Factors - Cervical Cancer
Sexually transmitted agents

Chlamydia trachomatis
Trichomas vaginalis
Sperm
HSV-2, CMV
Human papillomavirus
Cervical Cancer Precursors
Evidence that they exist

Spatial relationships
Temporal relationships
Molecular and risk factor relationships

Spatial Relationship

Invasive Cervical Cancer

Adjacent Epithelium
Cervical Cancer Precursors
Temporal relationships

Intraepithelial lesions identified years before women developed invasive cervical cancer

Model developed at other sites - *oral*

Cervical Intraepithelial Neoplasia
Continuum Concept

The CIN terminology stressed that all lesions formed a biologic continuum and all had potential to progress

*Widely accepted - easy since all CIN's needed treatment!*
Mild Dysplasia or CIN 1

Moderate Dysplasia or CIN 2
Severe Dysplasia or CIN 3

Carcinoma in-situ - Also called CIN 3
Pathology of the Cervix

Topics to Consider

Burden of cervical cancer
Epidemiology of cervical cancer
HPV - associations with cervical cancer and natural history
Papillomaviruses

Taxonomic family is *Papillomaviridae*

Highly diverse and occur in almost all mammals and birds

Classified on species specificity and degree of DNA relatedness

Nearly 100 human Papillomavirus (HPV) types have been identified

De Villiers et al. Virology:2004

Bovine   Equine
Phylogenetic Associations

Anogenital types of HPV

De Villiers et al. (2004) Virology
Munoz et al. (2006) Vaccine

Human Papillomaviruses

Lessons from phylogenetic studies

HPV 16 & 18 probably evolved in Africa and predate the speciation of Homo sapiens 200,000 years ago

HPV diversify very slowly - barely any molecular change accumulates over centuries or a few millennia

Bernard, H-U Trends in Microbiology. 1994
HPV Associated Diseases

Types of anogenital lesions

Cancers and cancer precursors of:

- cervix
- vulva
- vagina
- penis
- anus
- perianal skin

Genital warts involving all of the above sites

Anogenital HPV Types

- 6, 11: Condyloma
- 16, 18, 31, 33, 45, 52, 58: CIN 2,3, cancers
- 51, 53: CIN, rare cancers
- 42, 43, 44: CIN 1, flat penile
Papillomaviruses

Infect mucosal and cutaneous epithelium and produce benign warts or papillomas

Specific for target epithelium

Circular DNA genome of about 8,000 nucleotides divided into two regions:

- **early region** - viral replication
- **late region** - viral capsid

**HPV Genome**

- URR
- E6
- E7
- L1
- L2
- E5
- E2 / E4
- E1
HPV and Cervical Cancer

Evidence HPV is essential

- Molecular studies of cervical cancers
- Case-control studies of women with cancers and age-matched controls
- Prospective follow-up studies
- Experimental evidence

A huge number of studies have tested cervical cancers for specific types of high-risk HPV using sensitive PCR methods.

Results differ slightly from area to area, but overall conclusions are similar.

Over 95% of cervical cancers are associated with high-risk types of HPV.
HPV and Cervical Cancer

*International case-control studies*

Women with cervical cancer and age-matched controls without cancer

Tested for specific “high-risk” HPV types

Extraordinarily high odds-ratios for cervical cancer associated with infection with “high-risk” HPV types

Munoz *et al.* NEJM 2003

**Risk with Specific Types**

<table>
<thead>
<tr>
<th>HPV Type</th>
<th>Cancers</th>
<th>Controls</th>
<th>O.R.</th>
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<tbody>
<tr>
<td>HPV 16</td>
<td>53%</td>
<td>3.0%</td>
<td>434</td>
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<tr>
<td>HPV 18</td>
<td>11%</td>
<td>1.0%</td>
<td>248</td>
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<tr>
<td>HPV 45</td>
<td>4%</td>
<td>0.5%</td>
<td>197</td>
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<tr>
<td>HPV 31</td>
<td>3%</td>
<td>0.6%</td>
<td>123</td>
</tr>
<tr>
<td>HPV 52</td>
<td>2%</td>
<td>0.2%</td>
<td>200</td>
</tr>
<tr>
<td>HPV 33</td>
<td>2%</td>
<td>0.2%</td>
<td>373</td>
</tr>
</tbody>
</table>

Munoz *et al.* (2003) NEJM
HPV and Cervical Cancer
*Putting risk into perspective*

Risk of cervical cancer if HPV 16 (+) positive compared to HPV 16 (-) is 434

Risk of lung cancer in U.S. white male smoker compared to non-smoker is only 8

*Risk of breast cancer with HRT in Women’s Health Initiative only 1.3*

Natural History of HPV Infections

Wright and Schiffman (2003) NEJM
Exposure & Infection with HPV
Follow-up study of college women

553 Seattle-based college students with a mean age of 19 years
Underwent HPV DNA and Pap testing every 4 months for up to 5 yrs
Mean follow-up was 41.2 mos

Winer et al. (2003) Am J Epidemiol

Exposure & Infection with HPV
Follow-up study of college women

At entry 19.7% already HPV positive
Over 2 yrs, 39% of women initially HPV DNA negative became HPV positive
High-risk types of HPV were most common - 16, 18, 51, 56, 33, 35, 39

Winer et al. (2003) Am J Epidemiol
Development of HPV DNA Positivity

60% of the college students became HPV DNA positive by 2 years of follow-up and 80% became positive with increased follow-up.

Impact of HPV Globally

Prevalence of HPV infections

In most countries, HPV is the most common sexually transmitted infection in both males and females.

Because most individuals become infected within several years of initiating sexual intercourse and most infections are transient - prevalence is highest in young sexually active individuals.
### HPV Productive Infection or CIN 1

### Persistence of HPV Infections

<table>
<thead>
<tr>
<th>Author</th>
<th>Age</th>
<th>Type</th>
<th>% Persistent @ Mo</th>
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<tbody>
<tr>
<td>Woodman</td>
<td>20</td>
<td>Incid</td>
<td>4</td>
</tr>
<tr>
<td>Moscicki</td>
<td>20</td>
<td>Prev</td>
<td>30</td>
</tr>
<tr>
<td>Ho</td>
<td>20</td>
<td>Incid</td>
<td>30</td>
</tr>
<tr>
<td>Sun</td>
<td>34</td>
<td>Inc / Prev</td>
<td>35</td>
</tr>
<tr>
<td>Ahdieh</td>
<td>32</td>
<td>Inc / Prev</td>
<td>36</td>
</tr>
<tr>
<td>Richardson</td>
<td>23</td>
<td>Incid</td>
<td>62</td>
</tr>
</tbody>
</table>
World-wide Age-specific Prevalence of Cervical HPV DNA in Women

De Sanjose et al. in preparation - 2007

Development of CIN 2,3
Seattle - college students

36 mo cumulative risk of CIN 2,3:

- any incident HPV 11%
- incident HPV 16 or 18 27%

Median time to detection of CIN 2,3 was only 14 mos after HPV detection

Winer et al. (2005) J Inf Diseases
Development of CIN 2,3 in Seattle Study

- **HPV 16 or 18**: 27%
- **Other HPV types**: 10%

Percentage of Women vs. Length of Follow-up (months)

Winer et al. (2005) J Inf Diseases

Natural History of HPV Infections

Wright and Schiffman (2003) NEJM
Pathology of the Cervix

Topics to Consider

Burden of cervical cancer
Epidemiology of cervical cancer
HPV - associations with cervical cancer and natural history
Cervical cancer screening - secondary prevention

Cervical Cancer Prevention

Why screening works

Cervical cancer arises from precursor lesions called high-grade cervical intraepithelial neoplasia or CIN 2,3

Studies done 40 yrs ago showed that it takes on average 10 yrs to progress from a high-grade precursor to invasive cancer
Development of Cervical Cancer

High-grade Precursor  Invasive Cancer

Takes 10 years on average

High-grade Precursor  Invasive Cancer

Can be treated with simple outpatient methods that are highly effective at preventing cancer from developing.

Fully malignant lesion. Can have lymph node and distant metastases. Significant risk of death.
Cervical Cancer Prevention
Our current screening program

Identify precursor lesions and treat them in order to prevent the subsequent development of invasive cervical cancer

This is considered secondary prevention since we are not actually impacting the cause of the cervical cancer

Conventional Pap Test

Introduced by Babes and Papanicolaou in 1920's

Became widely adopted in industrialized countries beginning in the 1950's

Reduced cervical cancer dramatically

Dr. George M. Papanicolaou 1883-1962
Cervical Cancer Prevention

Current approach

Women are screened with cytology and those with abnormal cytology (*with or without high-risk HPV DNA testing*) undergo evaluation using colposcopy.

High-grade precursors are eliminated using outpatient treatment modalities.

*Prevents progression to invasive cancer*

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**Age-specific Incidence Rates of Cervical Cancer in Brazil and UK**

![Graph showing incidence rates](image)

Professor Xavier Bosch
**Pathology of the Cervix**

*Topics to Consider*

- Burden of cervical cancer
- Epidemiology of cervical cancer
- HPV - associations with cervical cancer and natural history
- Screening for cervical cancer - *secondary prevention*
- HPV vaccines - *primary prevention*

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**Final Immunogenicity Results for Phase IIb HPV 16 Vaccine Study**

- **HPV 16 L1 VLP Vaccine**
- **Placebo recipients who were HPV 16 Sero(+) / PCR(-) at Day 1**

Mao et al. (2006) Obst Gynecol
Prophylactic Vaccines

Current status

Merck quadrivalent HPV 6, 11, 16, 18 vaccine is widely approved for use in women

Recommendations for use of quadrivalent vaccine available in a number of countries

GSK bivalent HPV 16, 18 vaccine is now approved for use in E.U. and Australia - not yet approved for use in the U.S.

Summary of Large Vaccine Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>No Women Vaccine</th>
<th>No Women Placebo</th>
<th>FU</th>
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<tbody>
<tr>
<td>Koutsy, 2007</td>
<td>6,11,16,18</td>
<td>6087</td>
<td>6080</td>
<td>3 yr</td>
</tr>
<tr>
<td>Ault, 2007</td>
<td>6,11,16,18</td>
<td>10291</td>
<td>10292</td>
<td>3 yr</td>
</tr>
<tr>
<td>Garland, 2007</td>
<td>6,11,16,18</td>
<td>2241</td>
<td>2258</td>
<td>3 yr</td>
</tr>
<tr>
<td>Joura, 2007</td>
<td>6,11,16,18</td>
<td>7811</td>
<td>7785</td>
<td>3 yr</td>
</tr>
<tr>
<td>Harper, 2006</td>
<td>16,18</td>
<td>481</td>
<td>470</td>
<td>4-5 yr</td>
</tr>
<tr>
<td>Paavonen, 2007</td>
<td>16,18</td>
<td>7788</td>
<td>7838</td>
<td>15 mo</td>
</tr>
</tbody>
</table>

### Summary of Large Vaccine Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Endpoint</th>
<th>Vaccine Efficacy</th>
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</thead>
<tbody>
<tr>
<td>Koutsy, 2007</td>
<td>CIN 2,3/AIS</td>
<td>98% (68-100%)</td>
</tr>
<tr>
<td>Ault, 2007</td>
<td>CIN 2,3/AIS</td>
<td>99% (93-100%)</td>
</tr>
<tr>
<td>Garland, 2007</td>
<td>CIN 2,3/AIS</td>
<td>100% (94-100%)</td>
</tr>
<tr>
<td>Joura, 2007</td>
<td>VIN 2,3/ValIN 2,3</td>
<td>100% (72-100%)</td>
</tr>
<tr>
<td>Harper, 2006</td>
<td>CIN 1+</td>
<td>100% (42-100%)</td>
</tr>
<tr>
<td>Paavonen, 2007</td>
<td>CIN 2,3</td>
<td>90% (53-99%)</td>
</tr>
</tbody>
</table>


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### Pathology of the Cervix

**Topics to Consider**

- Burden of cervical cancer
- Epidemiology of cervical cancer
- HPV - associations with cervical cancer and natural history
- Cervical cancer screening - *secondary prevention*
- HPV vaccines - *primary prevention*