Cervical Cancer Screening and Prevention

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No commercial disclosures for this lecture

Cervical Cancer Screening

• Most successful cancer screening program in the US
  – 70% reduction in cervical cancer deaths in past 60 years
• Most expensive cancer screening program in the US
• Long-standing public health messages drive consumers behaviors, beliefs, and preferences
• Advances in cervical cancer prevention
  – Evidence based cytology screening intervals
  – Cytology technology: liquid-based cytology (LBC)
  – Adjunctive test modalities: HPV-DNA testing
  – Primary prevention through HPV vaccination

The BIG Picture

ACOG Practice Bulletin No. 109, Dec 2009

• Half of women in whom cervical cancer is diagnosed each year have never had cervical cytology testing
  – Plus 10% not screened within 5 years of diagnosis
• Response: increase cancer screening rates among women who are not screened or screened infrequently
  – Immigrants from countries where cytology screening is not the norm are an especially high-risk group
Case 1
36 year old woman screened recently with co-testing (HPV-DNA test + cytology)
The result returned high risk HPV negative and cytology negative
When would you have her return for her next screen?
1. 1 year
2. 2 years
3. 3 years
4. 5 years

Evolution of Cervical Cancer Screening Intervals
- **1940-1989**: annual “Pap smear” for all women
  - Linkage of “annual Pap smear” to “annual health exam”
- **1987**: Walton Commission (British Columbia)
  - Cytology screening every 3 years
- **1989**: AMA, ACOG, AMWA Consensus Statement
  - Annually, starting @ sexual activity or 18 years old
  - After 3 neg smears, testing may be done less frequently
  - *Longer intervals based on the absence of risk factors*

Designing Cytology Screening Intervals
- Screening *interval* of any test depends upon
  - Error rate of screening test (less sensitive $\rightarrow$ more often)
  - Progression rate of disease (faster transit $\rightarrow$ more often)
- Cervical cancer *risk factors* don’t impact interval
  - (Slow) rate of growth of pre-invasive the same, irrespective of behavioral risk factors
  - When transit time is faster (e.g., HIV positive, immunocompromise), then screen more often

Evolution of Cervical Cancer Screening Intervals
- **2002**: American Cancer Society
  - Start screening 3 years after first intercourse or at 21 y.o.
  - Stop after hysterectomy for benign disease & at 65-70 y.o.
    - if 3 normal and no abnormal results in the prior 10 years
  - Everyone else: every 2-3 years
  - Inform virginal women of screening “benefits and harms”
  - If co-testing (HPV+ cytology) result is negative/negative, re-screen “no earlier than every 3 years”
HPV DNA + Cytology ("Co-testing")
Wright, Obstet Gynecol 2004;103:304

Indications
- Women 30 years old and older
- Immunocompetent
- Cervix in place

- Improves sensitivity over cytology alone or HPV-DNA alone
- Very high negative predictive value; screen women who are HPV negative/cytology negative “no earlier” than 3 years

### Cervical Cytology Guidelines
ACOG Practice Bulletin #109 (2009)

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women under 21 yrs old</td>
<td>Avoid screening (regardless of age or other risk factors)</td>
</tr>
<tr>
<td>21-29 years old</td>
<td>Screen every 2 years</td>
</tr>
<tr>
<td>30 to 65 or 70 years old</td>
<td>May screen every 3 years</td>
</tr>
<tr>
<td>65 or 70 years old and older</td>
<td>May discontinue screening</td>
</tr>
<tr>
<td>HIV-positive</td>
<td>Screen annually</td>
</tr>
<tr>
<td>Immunosuppressed</td>
<td></td>
</tr>
<tr>
<td>Exposed in utero to DES</td>
<td></td>
</tr>
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</table>

### Why Start Cervical Cytology at 21?

- Most HPV infections are transient
- When HPV infection persists, transit to cancer is quite long
- Spontaneous regression of low grade lesions is common
- Invasive cervical cancer is very rare in 15-19 years olds
  - 14 cervical cancers annually
  - 1-2 cases per 1 million women
- In teens, screening does not reduce mortality
  - Cervical cancer rates have not changed since 1973-1977, before practice of screening at 18 or first intercourse

ACOG Practice Bulletin No. 109, Dec 2009
USPSTF Cervical Cytology Guidelines
March 2012

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<tr>
<td>• Cytology only, 21 to 65 years old</td>
<td>A</td>
<td>Every 3 years</td>
</tr>
<tr>
<td>• Cytology + HPV co-testing, 30-65 years old</td>
<td>A</td>
<td>Every 5 years</td>
</tr>
<tr>
<td>• Women under 21 yrs old</td>
<td>D</td>
<td>Avoid screening</td>
</tr>
<tr>
<td>• Age ≥65 with adequate prior screening and not high risk</td>
<td>D</td>
<td>Avoid screening</td>
</tr>
<tr>
<td>• Total hysterectomy; benign disease</td>
<td>D</td>
<td>Avoid screening</td>
</tr>
<tr>
<td>• HPV testing, alone or in combination, &lt; 30 years old</td>
<td>D</td>
<td>Avoid screening</td>
</tr>
</tbody>
</table>

Other Important Messages

- Women at any age should not be screened annually by any screening method
- For women 65 and older
  - “Adequate screening” is defined as...
    • 3 consecutively negative results in prior 10 years, or
    • 2 negative co-tests, most recently within 5 years
  - If screening stopped, do not restart for any reason
- Women who have been treated for CIN 2+ or AIS must be regularly screened for 20 years, even if 65 or older
  - With cytology alone Q 3 years or HPV+ cytology Q5 years

Summary of Important Guideline Changes

- 1st time that all 3 organizations involved with cervical cancer prevention have endorsed equivalent guidelines
- Co-testing is “ready for prime time” for women ≥ 30
  - But, co-testing every 5 years (NOT every 3 years)
- Women 21-29: cytology every 3 years (NOT 1 or 2)
- “3 consecutive documented negatives” no longer required
- Stop screening women under 21 years of age
- Stop screening women 65 and older if negative results and adequate prior screening

Triple A Guideline: ACS, ASCCP, Am Society for Clinical Pathology
CA CANCER J CLIN March 2012

<table>
<thead>
<tr>
<th>Age</th>
<th>Screening</th>
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<tr>
<td>&lt;21</td>
<td>No screening</td>
</tr>
<tr>
<td>21-29</td>
<td>Cytology alone every 3 years</td>
</tr>
<tr>
<td>30-65</td>
<td>Preferred: Cytology + HPV every 5 years* OR</td>
</tr>
<tr>
<td></td>
<td>Acceptable: Cytology alone every 3 years*</td>
</tr>
<tr>
<td>&gt;65</td>
<td>No screening, following adequate neg prior screens</td>
</tr>
<tr>
<td>After total hysterectomy</td>
<td>No screening, if no history of CIN2+ in the past 20 years or cervical cancer ever</td>
</tr>
</tbody>
</table>

*If cytology result is negative or ASCUS + HPV negative
Common Questions About Cytology Intervals

- Do virginal women need Pap smears?
- Are the intervals any different for women
  - With multiple sexual partners?
  - Using hormonal contraceptives, menopausal hormone therapy?
  - Who only have female partners?
  - Who are pregnant?
- If a cytology is not scheduled or necessary, what about the need to perform a screening bimanual pelvic exam?

Case 2

36 year old woman screened recently with co-testing (HPV-DNA test + cytology)

The result returned high risk HPV positive and cytology negative

What are her management options?

1. Repeat co-testing in 6 months
2. Repeat co-testing in 1 year
3. Reflex to a HPV 16/18 test (e.g., Cervista)
4. Colposcopy

Triple A: HPV Positive, Cytology Negative

- Occurs in 3.7% of women screened
- **Option 1:** repeat co-testing in 12-months
  - If co-test positive or LSIL+: colposcopy
  - If co-test negative or HPV-negative ASC-US: rescreen with co-testing in 5 years
- **Option 2:** reflex test for HPV16 or HPV16/18 genotypes
  - If HPV16 or HPV16/18 positive: colposcopy
  - If HPV16 or HPV16/18 negative: co-test in 12-months
    - Then manage as in option 1
- **Do not** immediately colposcope HPV positive/ cyto negatives

HPV Prevalence Pyramid

- 1% Clinical EGW
- 4% Sub-clinical HPV
- 10% HPV +, Colpo neg
- 60% HPV antibodies (prior infection)
- 25% Never Infected

HPV Infection From Time of First Sexual Intercourse

- Study of female college students (N=603)

Risk Factors for HPV infection

- **Sexual activity**
  - Time since onset of sexual activity
  - Number of sexual partners
  - Intercourse frequency
  - Presence of genital warts in sex partners
- **Condom use**
  - Some protection in men; inconclusive in women
- **Pregnancy**
  - EGWs more prevalent; often resolve after delivery
- **Cigarette smoking**
- **Immunosuppression**
  - HIV infection, organ transplant, steroids, cancer tx
  - Increases both HPV prevalence and viral load

HPV and Head and Neck Cancers

- Head and neck squamous cell carcinoma (HNSCC) includes oral cavity, oropharynx, hypopharynx, larynx, sinonasal tract, and nasopharynx
- 6th most common type of cancer in the world
- Risk factors: smoking, alcohol use, and betel chewing
- HPV infection, with dominance of *HPV16* infection, now recognized as a risk factor for oral SCC
HPV Burden of Illness

<table>
<thead>
<tr>
<th>US: 2004-8</th>
<th>Avg annual # cases</th>
<th>% due to HPV</th>
<th>Cases 2° to HPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervix</td>
<td>11,967</td>
<td>96 %</td>
<td>11,500</td>
</tr>
<tr>
<td>Vulva</td>
<td>3,136</td>
<td>51 %</td>
<td>1,600</td>
</tr>
<tr>
<td>Vagina</td>
<td>729</td>
<td>64 %</td>
<td>500</td>
</tr>
<tr>
<td>Penis</td>
<td>1,046</td>
<td>36 %</td>
<td>400</td>
</tr>
<tr>
<td>Anus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Female</td>
<td>3,089</td>
<td>93 %</td>
<td>2,900</td>
</tr>
<tr>
<td>- Male</td>
<td>1,678</td>
<td>93 %</td>
<td>1,600</td>
</tr>
<tr>
<td>Oropharynx</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Male</td>
<td>2,370</td>
<td>63 %</td>
<td>1,500</td>
</tr>
<tr>
<td>- Female</td>
<td>9,326</td>
<td>63 %</td>
<td>5,900</td>
</tr>
</tbody>
</table>

33,369 HPV-Associated Cancers Per Year
26,000 HPV-Attributable Cancers Per Year

MMWR / April 20, 2012 / Vol. 61 (15): 258

HPV Vaccines

<table>
<thead>
<tr>
<th>Brand name</th>
<th>HPV types</th>
<th>3 doses</th>
<th>Age range</th>
<th>US Licensure</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV4</td>
<td>Gardasil™ (Merck)</td>
<td>16, 18, 6, 11</td>
<td>0, 2, 6 mos</td>
<td>16-26</td>
</tr>
<tr>
<td>HPV2</td>
<td>Cervarix™ (GSK)</td>
<td>16, 18</td>
<td>0, 1, 6 mos</td>
<td>15-25</td>
</tr>
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HPV-4 (Gardasil®): Types 6, 11, 16, 18

- FDA approved for (ages 9-26)
  - Females: prevention of CIN, VIN, VaIN, AIN, AIS, cervical, vulvar, vaginal and anal cancers; warts
  - Males: prevention of AIN, anal cancer, and warts
  - Caused by HPV Types 6, 11, 16, and 18

HPV-2 (Cervarix®): Types 16, 18

- FDA approved for use in females 9-25 yrs old for
  - Prevention of CIN 2 or worse
  - Adenocarcinoma in situ
  - Cervical cancer
- Caused by oncogenic HPV types 16 and 18
**HPV4 Study Design**

- Four placebo-controlled double blind randomized clinical trials of Gardasil
- Multinational study sites; 20,541 women enrolled
- **Baseline testing**
  - Sero-status for HPV 6/11/16/18: prior infection
  - Virus detection (HPV-DNA): current infection
  - Pap smear
- **Inclusion criteria**
  - 16-26 years old at enrollment
  - < 4 lifetime sexual partners

**HPV-4 Study Design**

- Median duration of follow-up: 2-4 years
- **Endpoints** (outcome indicators)
  - Histopathology (CIN, AIS, VIN, VaIN)
  - HPV DNA type in biopsy (16, 18 vs other HR HPV)
  - External genital warts
  - LEEP, cone biopsy procedures
  - Surgical excision of warts
- **Immunogenicity Bridging Study**
  - 4,229 women 16-26 years old
  - 1,121 women 9-15 years old
  - Geometric mean titers higher in younger women

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**“Best Case Scenario” Per Protocol Efficacy**

- Seronegative at entry to HPV type being followed
- HPV-DNA negative during vaccination phase
- All 3 injections completed
- No protocol violation
- Case counting 1 month after dose 3

**“Average Case Scenario” General Population Impact**

- Serostatus on day 1
  - 73% negative for all 4 types
  - 20% positive for 1 type
  - <1% positive for all 4 types
- Any HPV-DNA + during vaccination phase
- Any Pap ≥ ASC-US on day 1
- Protocol violators

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**HPV4 Efficacy* Studies**

**Vaccinated vs. Placebo**

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<tr>
<th>Efficacy against lesions at 3-4 years</th>
<th>Per Protocol</th>
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<tr>
<td>CIN 2/3 + AIS</td>
<td>100%</td>
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<tr>
<td>High grade vulvar (VIN), vaginal (VaIN) lesions</td>
<td>100%</td>
</tr>
<tr>
<td>All CINs + AIS</td>
<td>95.2%</td>
</tr>
<tr>
<td>Genital Warts</td>
<td>98.9%</td>
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*Only lesions due to vaccine HPV types; does not include disease due to non-vaccine HPV types

AIS: adenocarcinoma in situ
**HPV4 Efficacy* Studies**

**Vaccinated vs. Placebo**

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<th>Per Protocol</th>
<th>General population</th>
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<tbody>
<tr>
<td>CIN 2/3 + AIS</td>
<td>100%</td>
<td>39.0%</td>
</tr>
<tr>
<td>High grade vulvar (VIN), vaginal (VaIN) lesions</td>
<td>100%</td>
<td>69.1%</td>
</tr>
<tr>
<td>All CINs + AIS</td>
<td>95.2%</td>
<td>46.4%</td>
</tr>
<tr>
<td>Genital Warts</td>
<td>98.9%</td>
<td>68.5%</td>
</tr>
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*Only lesions due to vaccine HPV types; does not include disease due to non-vaccine HPV types*

AIS: adenocarcinoma in situ

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**HPV Vaccines: Safety Issues**

- Since VLP antigen (not virus), expect few problems
- Injection-site pain, swelling, reddness are common
  - Can be more severe than with other vaccines
- Pregnancy category B; no ▲ in congenital anomalies
- Can be used in immunocompromised patients
- Do not pre-screen for HPV-DNA shedding
- Continue routine cytology to screen for SILS due to non-vaccine strains of HPV (i.e., other than HPV 16/18)

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**HPPV: Adverse Events (VAERS)**

Adverse events occur more frequently than for other vaccines

- *Venous thromboembolic events*
  - Young women often use hormonal contraceptives so coincidental occurrences of VTE may be anticipated.
- *Syncope*
  - Reported rate: 8.2 events / 100,000 delivered doses
  - Be cautious about loss of consciousness, vasovagal reaction and potential for falls and contusions

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**Benefits of HPV Vaccines**

- Decrease ano-genital cancer cases and death rates
  - Reduce hysterectomies, radiation tx, infertility
  - Reduce loss of productive years of life
- Decrease need for colposcopy, treatment of SIL
  - Fewer false positive cytology tests
  - Less detection and treatment of *pseudodisease* (non-progressive high grade CIN)
- Decrease cases of external genital warts (HPV4 only)
  - Less physical discomfort, stigmatization, cost

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Slade BA et al JAMA 2009;302:750-757
Decrease Cervical Cancer Rates

- 2009 US rates of cervical cancer
  - Incident cases per year: 9,710
  - Deaths: 3,700
- HPV vaccine will not prevent all of these cases
  - Some US women will choose not be vaccinated
  - Many immigrant women will not be vaccinated
  - Some develop cervical cancer even if vaccinated
- Conclusions
  - “Vaccine saves women’s lives”
  - “Vaccine for a cancer that already has been successfully controlled in the US”

Reduce (Unnecessary) Evaluation and Treatment

- There is a high rate of false positive cytology tests
  - ASC-US cytology: 3-10% have CIN 2/3+
  - LSIL cytology: 10-20% have CIN 2/3+
- Vaccine expected to sharply reduce transient HR-HPV infections that cause abnormal cytology tests
  - But, the false positives do not become cancer
- Conclusions
  - “Vaccine prevents invasive diagnostic evaluation”
  - “Vaccine prevents a false positive test result”

Decrease External Genital Warts

- Prevalence: 1% reproductive aged women
- US Incidence: 0.4% (1 case /250 persons/ year)
- Burden of illness
  - Many asymptomatic cases; no treatment needed
  - Can be cosmetically ugly; anxiety-provoking
  - Rare case requires surgery
- Conclusions
  - “Vaccine prevents a common, significant infectious disease and clinical problem”
  - “Vaccine prevents a cosmetic condition”

Vaccination of Boys and Men: Why??

- HPV-associated cancers in men include anal, penile, and oropharyngeal cancers; mainly due to HPV 16
- 2009: HPV4 licensed in males to prevent genital warts
- 2010: FDA added prevention of anal cancer in males (and females) as an indication for use
- Since 2006, HPV vaccine coverage in females has increased but remains low
  - In 2010, coverage with ≥ 1 dose among females aged 13-17 years was 49%; 3-dose coverage was 32.0%
**Advisory Committee on Immunization Practices (ACIP) CDC**

<table>
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<tr>
<th>Gender and Age</th>
<th>HPV-2 vaccine</th>
<th>HPV-4 vaccine</th>
</tr>
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<tbody>
<tr>
<td>Females 9-26*</td>
<td>Recommends</td>
<td>Recommends</td>
</tr>
<tr>
<td>Males 9-21*</td>
<td>No recommendation</td>
<td>Recommends**</td>
</tr>
<tr>
<td>Males 22-26</td>
<td>No recommendation</td>
<td>May be vaccinated</td>
</tr>
</tbody>
</table>

* Ideally at age 11 or 12 years old
** Updated by ACIP on 12/23/2011

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**Vaccines for Children (VFC) Program**

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<th>HPV-4 vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females 9-18 years*</td>
<td>Eligible</td>
<td>Eligible</td>
</tr>
<tr>
<td>Males 9-18 years*</td>
<td>Not eligible</td>
<td>Eligible</td>
</tr>
</tbody>
</table>

* Ideally at age 11 or 12 years old

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**American Cancer Society: 2007**

CA Cancer J Clin 2007;57:7

- Routine vaccination recommended for girls 11-12 yo
- Females as young a 9 can receive HPV vaccination
- HPV vaccination also is recommended women 13-18 to catch-up missed vaccine or to complete the series
- Not recommended for women >26 years old or men
- Insufficient data to recommend for or against universal vaccination of females 19-26 years old*
- Studies showed limited reduction in CIN 2+
- No data in women with >4 lifetime sexual partners
- Lack of cost-effectiveness analyses

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**American Cancer Society Recommendations**

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</tr>
<tr>
<td>Males</td>
<td>No recommendations for males of any age</td>
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