Cervical Cancer: Screening and Prevention

Pacific Regional Comprehensive Cancer Control Program
University of Hawaii Department of Family Medicine and Community Health
June 9, 2008
Intended Audience

- Physicians
- Public health nurses performing cervical cancer screening
Learning Objectives

Upon conclusion of this educational activity, the participant will be able to:

- Discuss the role of human papillomavirus (HPV) infection and the development of cervical cancer
- Describe different screening methods for the prevention of cervical cancer
- Discuss the role of HPV vaccination in preventing cervical cancer
Why do we care about cervical cancer?

- 2nd most common cancer worldwide
- 500,000 cases worldwide
- 275,000 deaths
- More than 80 percent of the cases are in the developing world
- Lifetime risk of developing cervical cancer in the developing world is 2-4 percent
Figure 1. Estimated number of cases and incidence of cervical cancer

Source: Ferlay et al.²
Cervical cancer strikes at a young age

- Cervical cancer strikes between ages 35 to 55
- By comparison:
  - Lung cancer average age is 69
  - 90 percent of colon cancers occur after the age of 50
  - Breast cancer average age is 62
  - Prostate cancer average age is 68-70
More advanced disease

- More likely to be advanced disease at time of detection
- Cervical cancers are diagnosed at younger ages and more advanced stages in Micronesian, Marshallese, and American Samoan women living in the U.S. Associated Pacific Islands (USAPI) than in U.S. white women
- 50 percent mortality rate
- Treatment options often unavailable
Risk Factors

- HPV infection
- Lack of screening
- Tobacco use
- Early onset of sexual activity
- Multiple sexual partners over time
- Multiparity
- Long-term use of oral contraceptives
- Immunosuppression
- History of sexually transmitted infection (STI)
- Circumcision has protective effect for transmission of HPV
Signs and Symptoms

- Abnormal vaginal bleeding
- Postcoital bleeding
- Vaginal discharge
- Pelvic or lower back pain
- Hematuria
- Hematochezia
Human Papillomavirus (HPV)

- HPV infects the epithelium of skin and mucous membranes
- When a persistent HPV infection occurs at a transformation zone between different kinds of epithelium, cancer can develop
- These zones exist in the cervix, anus, and oropharynx
- HPV infection necessary to cause cervical cancer
Cervical Transformation Zone

- Most distal cervical crypt opening
- Squamocolumnar junction
- Area of ectopy

Source: J Midwifery Womens Health © 2004 Elsevier Science, Inc.
HPV

- 118 types classified
- 30 types associated with cervical cancer, 15 of which cause almost all cancers
- Types 16 and 18:
  - Cause 70 percent of all cervical cancers
  - Cause 50 percent of all CIN3
- Types 6 and 11:
  - Cause 90 percent of all genital warts
HPV infections

- Estimated that 6.2 million people in the U.S. are newly infected with HPV each year.
- 20-30 percent of women have infection with multiple strains.
- So why are there so many people infected, but much fewer cervical cancers?
HPV and the immune response

- Most cervical HPV infections are cleared or suppressed in 1-2 years
  - Clearance occurs through:
    - Desquamation of epithelial cells
    - Cell-mediated immunity
    - Neutralizing antibodies
  - Smoking
  - Average time is 12 months
    - 75-90 percent within 1 year
  - This includes those with cytologic abnormalities
- Data from older women and HIV patients suggests that many infections are suppressed rather than cleared
Cervical Cancer Development

- Infection
  - Cervical transformation zone

- Persistence
  - Virus not cleared

- Precancer
  - Normal epithelium replaced by undifferentiated cells

- Invasion
  - 20-30 percent of precancers invade over 5-10 years
Types of Cervical Cancer

- Squamous cell - 70 percent
- Adenocarcinoma - 25 percent
- Adenosquamous - 3 to 5 percent
Preventing Cervical Cancer

- Screening for precancer or high-risk HPV
  - Looks for evidence of infection by analyzing cells, cervical appearance, or DNA
  - Affects persistence and precancer stage

- Primary prevention through vaccination
  - Vaccine given before infection
  - Prevent persistence stage
What is cancer screening?

- Aimed at detected cancer early, when treatment may be easier, more effective and available on-island
- Testing for early forms of disease before symptoms occur
- Need a reliable early detection test
- Tests a large number of healthy people to identify those with a high probability of having clinically unrecognized cancer or precancerous lesions.
Screening Techniques

- Papanicolaou (Pap) smear (cytology-based)
- Visual inspection with Acetic Acid (VIA) or with Lugol’s Iodine (VILI)
- HPV DNA detection
Barriers to screening

- Cultural
- Unaware of importance
- Lack of resources
  - Equipment and supplies
  - Laboratory
  - Funding
  - Trained professionals
  - Female health professionals
Pap smears

- Cells taken from transformation zone and endocervical canal are analyzed for histologic changes associated with precancer
- Conventional: samples obtained by brush and spatula are plated on a microscope slide
- Liquid-based: samples obtained by brush are placed in liquid medium and spun in lab to plate only a monolayer
  - Can also test for gonorrhea, chlamydia and HPV
Pap smears

- 50-60 million Pap smears are done in the U.S. each year
- 3.5 million of these are classified as abnormal
- 2.5 million of these women undergo colposcopy
## Pap smear results

<table>
<thead>
<tr>
<th>Bethesda Classification</th>
<th>WHO classification</th>
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</thead>
<tbody>
<tr>
<td>Atypical squamous cells (ASC)</td>
<td>Squamous atypia</td>
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<tr>
<td>Undetermined significance (ASCUS)</td>
<td></td>
</tr>
<tr>
<td>Cannot exclude high-grade SIL</td>
<td></td>
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<tr>
<td>LSIL (low-grade squamous intraepithelial lesions)</td>
<td>Cervical intraepithelial neoplasia (CIN) 1</td>
</tr>
<tr>
<td>HSIL (high-grade squamous intraepithelial lesions)</td>
<td>CIN 2, CIN 3, carcinoma <em>in situ</em></td>
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</table>
Pap smear results

- Only one-third of women with HPV by DNA testing have pathology seen on Pap.
- CIN 2 can be produced by types of HPV that are not carcinogenic.
  - Equivocal
- CIN 1 is very insensitive
  - Does not predict a higher risk of CIN 3 than a negative biopsy
Pap smears

- Sensitivity: 60 percent
- Specificity: 95 percent

Review:
- Sensitivity-probability that a person with the disease will test positive. It equals the number of people with positive tests over the number of people with the disease
- Specificity-probability that a person without the disease will test negative. It equals the number of people with a negative test over the number of people without disease
Pap smears

Pros:
- Have dramatically reduced the incidence of cervical cancer in many developed countries
- Most specific

Cons:
- Requires laboratory infrastructure
- Requires highly-trained cytotechnologists
- Extensive workup of abnormal results
- Treatment occurs later
- Least sensitive
Diagnostic problems and pitfalls

http://screening.iarc.fr/atlaspitfall.php
Direct visual inspection

- Apply 3-5 percent acetic acid (VIA) or Lugol’s iodine (VILI) to cervix
- Inspect with naked eye or magnifying device to look for changes associated with precancer
- Developed in 1930s, before cytology-based screening
- Proven effective in reducing cervical cancer
- Many ongoing international trials and training
  http://screening.iarc.fr/study_major.php?lang=1
IARC Clinical Reference Chart for VIA

VIA NEGATIVE
- No definite acetowhite area
- Acetowhiteness of the mucus on columnar epithelium
- Mucus plug
- Nabothean cysts
- Polyp
- Acetowhite area far away from SCJ

VIA POSITIVE
- Well-defined, acetowhite lesions touching the SCJ or close to the os
- Acetowhiteness on the entire cervix

CANCER
- Acetowhiteness of growth on the cervix
- Acetowhiteness of growth on the cervix; partly obliterated by bleeding

Direct visual inspection (DVI) 
(Visual Inspection with Acetic Acid [VIA])

- Sensitivity: 68 percent
- Specificity: 85 percent

- Sensitivity varies by provider and by standard applied for treatment (65-96 percent)
- Likely lower sensitivity outside of research institutions
Direct visualization

- **Pros:**
  - Screen-and-treat at same visit
  - Low cost
  - Does not require close follow-up (rescreen in 1 year if initial positive screen & treat)
  - Do not need lab infrastructure

- **Cons:**
  - Sensitivity varies by person
  - Squamocolumnar junction (SCJ) moves inward with increased age
HPV DNA testing

- Samples collected from cervix are tested for presence of high-risk strains of HPV
- Can also be collected by the patient
HPV DNA testing

- Sensitivity: 84 percent
- Specificity: 88 percent

- Sensitivity for patient-collected specimen: 67 percent
- Specificity for patient-collected specimen: 83 percent
HPV DNA testing

**Pros:**
- Detects this high risk strains of HPV which cause almost all cervical cancers
- Can be self-collected
- Greatest reproducibility
- Most sensitive

**Cons:**
- More costly than DVI
- Most likely requires 2 visits
- Rapid, low-cost HPV DNA test being developed by Program for Appropriate Technology in Health (PATH)
Screening Comparison

- Most effective: HPV DNA testing
  - 27 percent cancer risk reduction
- Most cost-effective: DVI
  - Saves money compared to not screening
  - 26 percent cancer risk reduction
Screening Guidelines

- United States Preventive Services Task Force (USPSTF)
  - Screen women who have been sexually active and have a cervix
  - Start screening at age 21, or 3 years after the onset of sexual activity (whichever comes first)
  - Stop screening at age 65, and women who have had a hysterectomy for benign disease
  - Screen at least every 3 years
  - Insufficient evidence to recommend for or against liquid-based cytology, computerized rescreening, or HPV DNA testing as primary screening modality
Primary Prevention

- HPV vaccine
  - Two currently available:
    - Gardasil
      - HPV 6, 11, 16, 18
      - Approved in U.S. and several other countries
    - Cervarix
      - HPV 16, 18
      - Approved in Australia
  - Others in development
    - More than 4 types
HPV Vaccines

- Virus-like particle (VLP) vaccine
- Inject recombinant L1 protein as non-infectious capsid
- No genetic material
- Antibody response 20-50 times as high as that induced by natural infection
HPV Vaccines

- Data currently shows vaccine effect for more than 5 years
  - Studies being done to demonstrate 10 year efficacy
- Efficacy 95 percent in those not receiving all doses of vaccine
- Generally safe and well-tolerated
  - Fever and pain at injection site most common complaint
HPV Vaccines

- Do not treat current infections

- Only prevent future infections
  - Limits usefulness in older populations who are already sexually active
Gardasil

- 3 doses, at 0, 1, and 6 months
- Cost roughly $120 per dose
- Recommended ages: 9-26
  - Advisory Committee on Immunization Practice and American College of Obstetricians and Gynecologists
  - Note: If women 15 to 26 are to be immunized, program must consider what % of these women are already infected with HPV 16, 18 (vaccine not as effective in these women). If a significant portion—will need to think through strategy.
Questions about HPV vaccines

- How well does it work with fewer than three doses?
- How long is the duration of protection?
- Will boosters be needed?
- Are they effective in men?
- What about the other oncogenic HPV types that aren’t covered?
- Do we revaccinate the covered cohorts when new vaccines come out that protect for more than 4 HPV types?
HPV Vaccines

Pros:
- Nearly 100 percent protection against precancer and cancer caused by most common high-risk strains
- Well-tolerated (although painful shots)
- Can be integrated as part of comprehensive cervical cancer screening program

Cons:
- Effect not seen for 20-30 years
- Cost of program implementation
- Sustainability in resource limited setting
- Questions still remain
- Only targets strains causing 70 percent of cancers
- Does not protect women already infected
- Still need good screening program
- Potential of creating expectation for health services and population that this is the “answer” for cervical cancer
Screening and Prevention

- Effectiveness
- Vaccination
- Screening
- Infection
- Persistence
- Precancer
- Invasion
Summary

- HPV infections in the transformation zone of the cervix lead to cervical cancer
- Cervical cancer risk factors include lack of screening, smoking, and history of STIs
- 4 steps to cervical cancer: infection, persistence, precancer, and invasion
- Screening for cervical cancer via cytology, DVI, or DNA testing can prevent cervical cancer
- Vaccinating against high-risk HPV can prevent cervical cancer
References

- http://www.rho.org (RHO Cervical Cancer)
- http://www.uptodate.com (UptoDate)
Additional Resources

Post-test

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<tr>
<th>Question</th>
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<tr>
<td>1. Most HPV infections lead to precancer.</td>
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<tr>
<td>2. The squamocolumnar junction moves into the endocervix with advancing age.</td>
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<tr>
<td>3. Lack of screening is a risk factor for cervical cancer.</td>
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<tr>
<td>4. The most cost-effective screening measure is Pap smears.</td>
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<td>5. The USPSTF recommends screening at least by age 21.</td>
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<td>6. HPV vaccines do not treat existing infections.</td>
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<tr>
<td>7. DVI always requires multiple visits.</td>
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<tr>
<td>8. Most cervical cancers are caused by HPV types 16 and 18.</td>
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<tr>
<td>9. Vaginal bleeding can be a symptom of cervical cancer.</td>
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<tr>
<td>10. HPV vaccines should be targeted at 25-35 year-olds.</td>
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