



**HPV Infections
and
Cervical Cancer**

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Objectives


- Describe at least four HPV related diseases
- Describe how HPV is transmitted
- Identify two potential strategies to help prevent certain HPV related diseases
- Describe current guidelines for cervical cancer screening




**The Faces of HPV Related
Cancer...**



Cervical Cancer: A Sexually Transmitted Disease.....




That Can Be Eliminated




Human Papillomavirus (HPV)

- A group of 150 different types of double stranded DNA viruses
- Persistent High Risk HPV infection is associated with development of anogenital cancers (40 Types)
 - Cervical
 - Vulvar
 - Vaginal
 - Anal
 - Penile


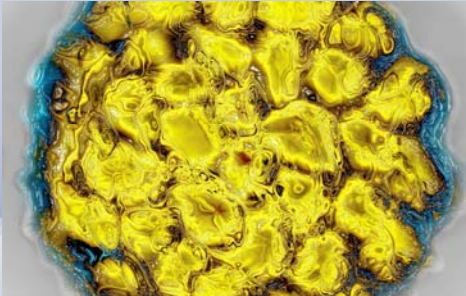


Human Papillomavirus

- Oropharyngeal Cancers
 - High Risk HPV
 - Association with tobacco and alcohol use
 - Tonsillar and base of tongue most common
- Anogenital Warts
 - Low Risk HPV (> 90 % type 6,11)
 - 360,000 cases last year
- Recurrent Respiratory Papillomatosis
 - Rare, significant morbidity, juvenile and adult onset. Low risk HPV (type 6,11)




HPV DNA



The Facts...

- HPV is the most common Sexually Transmitted Infection in the United States
 - 79 million Americans currently infected
 - 14 million new infections every year
 - 18,000 women and 9,000 men will develop HPV related cancers this year
 - Prior to the onset of vaccination, Economic Cost:
 - Prevention and Treatment \$8 Billion, the majority (\$6.6 billion) for cervical cancer screening and follow up



Cervical Cancer and HPV

- Virtually all Cervical Cancers are attributable to 13 types of HPV
- First identified cancer solely attributed to an infectious agent
- HPV Type 16 accounts for nearly 60% of cervical cancers and has the highest carcinogenic potential
- HPV 18, next at 10-15%



HPV Infection

- Can be transient in up to 70%
- Infection common in women in early 20s.
 - Cleared in an average of 8-24 months
- Persistence at 1 and 2 years highly predictive of precancerous changes on the cervix
 - Risk factors for persistence: cigarette smoking, multiple partners, compromised immune system, HIV positivity, Oral Contraceptive Pill use.
- Lifetime cumulative risk for women is 80%



Cervical Dysplasia

- Detection of dysplasia has been the rationale for screening for cervical cancer
- Low grade changes (LSIL, CIN 1) often transient, associated with HPV
- High grade changes (HSIL, CIN 2,3) result from persistent HPV infection
 - Considered precancerous change
 - Progression to cancer averages 8.1 -12.6 years
 - Treatment recommended



Transmission of HPV

- Genital - Genital contact
- Oral – Genital Contact
- Sexual Intercourse
- Maternal – Infant (intrapartum), rare
- More likely Female to Male

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Transmission of HPV

- Can be acquired in first sexual encounter
- Can result from non penetrative sexual contact
- If used correctly, condoms can reduce the risk of HPV infection
- Most infected individuals are unaware they are infected and unknowingly can transmit the virus

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George Papanicolaou

- Trained in Zoology and Medicine, Athens
- Secured a position at Cornell studying the menstrual cycle of Guinea Pigs
- Used a nasal speculum and Q tip, discovered that shapes and sizes of cells changed with the menstrual cycle

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Maria Papanicolaou

- Late 1920s, George needed human subjects...
- A hard to believe display of "Conjugal Fortitude", she agreed to Daily cervical smears
- Allowed George to prove what he found in the Guinea Pigs
- Led to speculation that if normal cells changed over time, would cancer cells do the same?



Twenty Year Hiatus

- George's theory was criticized by Pathologists
- He retreated to his lab for 20 years
- Returned with the premise that by looking at cervical cells, cancer could be detected in it's earliest stage
- Studies in the 1950s led to integration of the "Pap Smear" into women's health care, 1960s



The HPV Connection

- Dr Harald Zur Hausen
 - Suggested that the same viral particles found in genital warts may be associated with genital tract malignancies
 - 1983, isolated HPV 16 and implicated it's role in cervical cancer
 - 1984, discovered HPV 18
 - HPV 16, 18 responsible for 70% cervical cancers



Cervical Cancer Screening

- 1988, 1991, 2001
 - Developed evidence based guidelines for terminology and management of abnormal pap smears
- 2006
 - Identified strategies for + HPV and guidelines for adolescents
- 2012
 - Consensus group, analysis from a data base of 1.4 million women



2012: Evidence, Consensus, Change...

- 47 experts representing 23 professional societies
- Published evidence, research and trials
- New evidence from analysis of a clinical data base from Kaiser Permanente Medical Care
 - 1.4 million women followed for 8 years
 - Modified or validated prior guidelines
 - Size of data base allowed for age based recommendations and F/U of abnormalities.



Cervical Cancer Screening

- Cervical Cancer prevention is a process with benefits and harms
- Risk cannot be reduced to zero
- Attempts to achieve zero risk could result in overtreatment
- Optimal prevention strategy: identify and treat persistant HPV abnormalities most likely to progress to cancer



• Area of immature metaplasia between the original and current squamocolumnar junction (SCJ)¹

• ~99% of HPV-related genital cancers arise within the transformation zone of the cervix¹

1. Castle PE. *J Low Genit Tract Dis*. 2004;8:224-230.

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2012 Guidelines on Cervical Cancer Screening

- Key Areas of focus
 - Frequency of Screening
 - Age specific screening recommendations
 - Age specific guidelines for management of abnormalities
 - Combined use of Cytology and HPV (Co-Testing)

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Rationale for New Guidelines

- Most Dysplastic lesions are transient
- Long progression time from pre-invasive lesion to invasive cancer
- 0.1% of cervical cancer cases occur <21 yo
- Adverse effects of treatment (LEEP, excisional)
 - Preterm delivery 70 % increase
 - Low birth weight 82% increase
 - Premature rupture of membranes 169% increase
 - Lancet 2006 367:489-98

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**2012 Guidelines
Initiation of Screening**

- Screening begins at age 21
 - Prior to age 21, screening can lead to unnecessary and potentially harmful evaluation and treatment in women at very low risk for cancer

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2012 Guidelines

- Women age 21-29
 - Cytology (Pap Smears) Every 3 Years
 - Recommendation **Against** Co-Testing (many are +HPV)

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**2012 Guidelines
Frequency of Screening**

- Women age 30 -65
 - Co-testing with Cervical Cytology and High Risk Human Papillomavirus testing every 5 years
 - If HPV testing not available, then Cytology alone every 3 years
 - Recommendation based on 11 prospective studies with 1 year to 16 year follow up.
 - Reduction of cervical cancer in 2 RCTs
 - Rijkaart et al, Lancet Oncol 2012;13:78-88
 - Ronco et al, Lancet Oncol 2010;11:249-57

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2012 Guidelines on Cervical Cancer Screening

- Discontinue screening at age 65
 - If a history of adequate prior screening (3 consecutive normal paps within the last 10 years)
 - Unless prior CIN 2+, then co-test every 3 years for 20 years, even if > 65.
 - Do not resume if >65 yo even if new partner (ACS)
- Discontinue screening following hysterectomy
 - If no history of a high grade lesion




Prevention and Risk Reduction of HPV Related Disease

- Abstinence
- Mutually monogamous relationship
- Limiting number of sexual partners
- Consistent and correct condom use
- Tobacco avoidance
- Male circumcision




HPV Vaccines

- Two FDA approved three dose vaccines for prevention of HPV infection
- Gardasil- Quadrivalent Vaccine
 - Prevention of cancer and precancerous changes of the cervix, anus, vulva and vagina (HPV Types 16,18)
 - Prevention of genital warts (HPV Types 6,11)
 - Females and Males aged 9-26 years




HPV Vaccines

- Cervarix – Bivalent Vaccine
 - Prevention of cervical cancer, cervical intraepithelial neoplasia (CIN) 2 or worse
 - Prevention of adenocarcinoma in situ and CIN 1 caused by HPV Types 16,18
 - Females aged 9-25 years




HPV Vaccine

- Preventative, not a Treatment
- Maximum effectiveness achieved when given during the target ages (11 and 12 years) or prior to the onset of sexual activity
- Can be given regardless of HPV status (do not test!)
- In study participants who were HPV negative and followed protocol, the vaccine was 98.2% effective in preventing HPV 16,18 related CIN 2 and 3



HPV Vaccine

- Efficacy of the Quadrivalent vaccine against HPV 6, 11 related genital warts in women was 98.9%
- Efficacy of the Quadrivalent vaccine against vulvar (VIN) and vaginal (VAIN) dysplasia was 100%



HPV Vaccine

- Efficacy of Quadrivalent vaccine in Males
 - 90.4 % in preventing genital warts
 - Sub-study in a population of men who have sex with men, vaccine was 77.5% effective in preventing precancerous changes of the anus (AIN)
 - Led to FDA approval of the quadrivalent vaccine for the prevention of anal cancer and precursors caused by HPV 6, 11, 16, 18



Our Responsibility

- Educate our Patients and Parents
- Providers not recommending
 - Top reason given for not vaccinating for HPV
- Be aware of patients perceptions vs reality.
 - Seriousness of HPV infection
 - Concerns for safety
 - Efficacy
 - Perception of child as “low risk”



www.asccp.org/consensus2012

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