

Cervical Cancer Screening and Prevention

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- I have no significant relationships to disclose.

Outline

- Epidemiology of HPV and Cervical Cancer
- Current Screening Paradigms
- HPV Prevention

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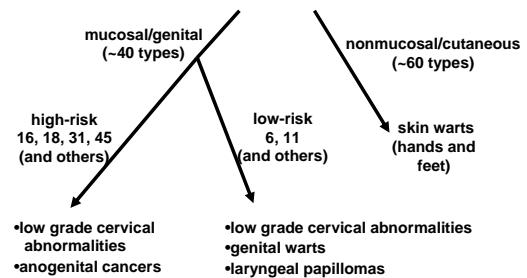
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Human Papillomavirus (HPV)

- Small DNA virus
- More than 100 types identified based on the genetic sequence of the outer capsid protein L1
- 40 types infect the mucosal epithelium

www.cdc.gov/vaccines/pubs/pinkbook/downloads/Slides/HPV11.ppt

Human Papillomavirus Types and Disease Association



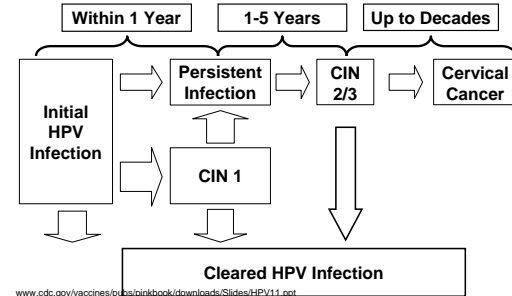
www.cdc.gov/vaccines/pubs/pinkbook/downloads/Slides/HPV11.ppt

HPV-Associated Disease

Type	Women	Men
16/18	70% of Cervical Cancer 70% of Anal/genital Cancer	70% of Anal Cancer Transmission to women
6/11	90% of Genital Warts 90% of RRP lesions	90% of Genital Warts 90% of RRP lesions Transmission to women

www.cdc.gov/vaccines/pubs/pinkbook/downloads/Slides/HPV11.ppt

Natural History of HPV Infection



www.cdc.gov/vaccines/pubs/pinkbook/downloads/Slides/HPV11.ppt

HPV Clinical Features

- Most HPV infections are asymptomatic and result in no clinical disease
- Clinical manifestations of HPV infection include:
 - anogenital warts
 - recurrent respiratory papillomatosis
 - cervical cancer precursors (cervical intraepithelial neoplasia)
 - Cancer (cervical, anal, vaginal, vulvar, penile, and some head and neck cancer)

www.cdc.gov/vaccines/pubs/pinkbook/downloads/Slides/HPV11.ppt

HPV Epidemiology

- **Reservoir** Human
- **Transmission** Direct contact, usually sexual
- **Temporal pattern** None
- **Communicability** Presumed to be high

www.cdc.gov/vaccines/pubs/pinkbook/downloads/Slides/HPV11.ppt

HPV Disease Burden in the United States

- Anogenital HPV is the most common sexually transmitted infection in the US
 - Estimated 20 million currently infected
 - 6.2 million new infections/year
- Common among adolescents and young adults
- Estimated 80% of sexually active women will have been infected by age 50
- Infection also common in men

www.cdc.gov/vaccines/pubs/pinkbook/downloads/Slides/HPV11.ppt

Cervical Cancer Epidemiology

	New Cases	Deaths
US (2011)	12,710	4,290
Worldwide (2008)	529,800	275,100

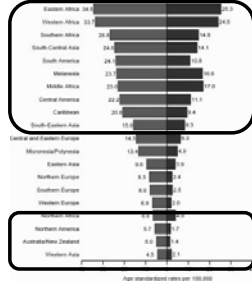
Worldwide

- Third most common cancer diagnosis in women
- Fourth most common cause of cancer death in women worldwide.

Cancer Facts and Figures, 2011. Available at: <http://www.cancer.org/Research/CancerFactsFigures/CancerFactsFigures2011-most-requested-tables-and-figures>. Accessed 9/9/2011.
A. Jemal, F. Bray, et al. CA: A Cancer J for Clin 2011; 61:69-90.

Epidemiology of Cervical Cancer: Worldwide

- Age distribution
 - 50% between 35-55
 - Rare under 20
 - 20% over 65
- Disproportionately affects racial groups
 - Hispanic
 - African American
- Worldwide problem:
 - 85% in developing world
 - 27% cancer deaths in India alone



K Robinson and DS Dixon; *DevRx Cervical Cancer*, 2011 (Jones & Bartlett); A. Jemal, F. Bray, et al. CA: A Cancer J for Clin 2011; 61:69-90.

Risk Factors

- First intercourse at an early age
- Multiple sexual partners
- Multiple pregnancies
- Smokers
- Prenatal exposure to DES
- Oral contraceptives?

Prognostic Factors (10 year SR)

- FIGO Stage
 - 85-90% early stage; 14% with metastatic disease
- Radiation dose to point A
 - 50% survival if not optimally dosed
- Overall time of Radiotherapy
 - 1% loss of tumor control/day of tx prolongation over 30 days
- Hemoglobin levels
 - 42% if transfused vs. 60% if none
- Squamous histology
 - Squamous: 61% OS; Non-squamous: 55% OS.
- Para-aortic node involvement
 - Average 5-year SR 40%

AW Fyles, M Pintile, et al. *Radiother Oncol* 1995; 35:107-17.

We can prevent cervical cancer

We can help women globally

Outline

- Epidemiology of HPV and Cervical Cancer
- Current Screening Paradigms
- HPV Prevention
- Worldwide Implications

2009 Screening Guidelines (ACOG)

- Pap smears beginning at 21 years old
 - Irregardless of sexual activity
 - Incidence of invasion is low
 - Rate of spontaneous regression is high
- Women > 30 in stable, monogamous relationship
 - Screening every 3 years is reasonable IF BOTH prior and High risk HPV test are negative
- Women > 30, three consecutive negative Pap tests AND no risk factors
 - Screen every 3 years
- Annual screen (or more) if high-risk:
 - HIV+, history of DES, prior CIN2/3, or cervical cancer

ACOG Practice Bulletin # 108, 12/2009.

Screening Methods for Cervical Cancer

- Pap Smear
- Liquid Based Cytology
- HPV Genotyping
- Colposcopy

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Papanicolaou Smear (Pap)

- Introduced in 1943
- Between 1955 and 1992, reduction in deaths by 74%
- When introduced to naïve populations, incidence of cervical cancer falls 60-90% within 3 years of implementation
- Causes of screen failure:
 - Improper follow-up (22-63%)
 - Interval progression (rare with annual screening; up to 50% with every 3 year)
 - Abnormalities not picked up (14-33%)
 - Sampling error (abnormal cells not collected)
 - Detection error (failure to identify as abnormal)

K Robison and DS Diaz; Dx/Rx Cervical Cancer, 2011 (Jones & Bartlett); USPSTF Screening Recommendations for Cervical Cancer. Available at: <http://www.ncbi.nlm.nih.gov/books/NBK42834/#A4194>).

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Liquid Based Cytology

- Thin-prep®
- Evaluated prospectively in 8636 Costa Rican women, using colposcopy for final diagnosis
- Compared to conventional cytology:
 - More women referred to colposcopy for ASCUS (13% vs 7%, p<.001)
 - Thin prep lead to detection of 93% HSIL (vs 78%) and 100% cancers (vs. 91%)
 - Highly sensitive (p<.001)
- Two further studies suggest increase detection of LSIL or higher abnormalities vs. conventional cytology.

ML Hutchinson, DJ Zahniser, et al. Cancer 1999; 87:48-55. USPSTF Screening Recommendations for Cervical Cancer. Available at: <http://www.ncbi.nlm.nih.gov/books/NBK42834/#A4194>).

Screening Methods for Cervical Cancer

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HPV Testing as a Screening Tool

Tested prospectively in 6 studies as a screening tool

Author (Year)	Country	N	Prevalence (%)					
			CIN1	LSIL	CIN2	CIN3	HSIL	CA
Cuzick (1999)	UK (screened)	2988	0.9		0.3	1.1		0
Petry (1999)	Germany	138 (HIV+)	14.5		3.6	6.5		2.2
Schiffman (2000)	Costa Rica	8544		2.2			1.5	0.14
Womack (2000)	Zimbabwe	466		12.9			12	0
Womack (2000)	Zimbabwe	2140		16.2			10	0.14
Wright (2000)	South Africa	1365		2.9			3.4	0.17

USPSTF Screening Recommendations for Cervical Cancer. Available at: <http://www.ncbi.nlm.nih.gov/books/NBK42834/#A4194>.

HPV Test: High-Grade

USPSTF Summary of Evidence

	All Patients	excl HIV+	Prevalence <10%
Total n	6793	6544	5425
Sensitivity	84.4	83.7	81.6
Specificity	78.7	79.9	78.2
Positive Predictive Value	23.4	23.3	18.2
Negative Predictive Value	98.5	98.5	98.6
Positive Likelihood Ratio	4.0	4.2	3.8
Negative Likelihood Ratio	0.2	0.2	0.3

USPSTF Screening Recommendations for Cervical Cancer. Available at: <http://www.ncbi.nlm.nih.gov/books/NBK42834/#A4194>.

HPV Test: Low-Grade

USPSTF Summary of Evidence

	All Patients	excl HIV+	Prevalence <10%
Total n	5674	5425	3068
Sensitivity	67.3	65.2	73.5
Specificity	80.1	81.2	90.5
Positive Predictive Value	36.7	35.7	29.2
Negative Predictive Value	93.4	93.6	98.5
Positive Likelihood Ratio	3.4	3.5	7.7
Negative Likelihood Ratio	0.4	0.4	0.3

USPSTF Screening Recommendations for Cervical Cancer. Available at: <http://www.ncbi.nlm.nih.gov/books/NBK42834/#A4194>.

HPV Test as a Screening Tool

Summary

- Good sensitivity
- Good negative predictive value
- Limitations of current literature:
 - Only one study performed in a screened population
 - No studies linked to outcomes thus far
- Thus: no role thus far of HPV Testing as a screening tool to replace cytologic evaluation *in routinely screened populations* (as in the US)

USPSTF Screening Recommendations for Cervical Cancer. Available at: <http://www.ncbi.nlm.nih.gov/books/NBK42834/#A4194>.

HPV Testing as a Triage Tool

American Society for Colposcopy and Cervical Pathology (ASCCP) recommends reflex HPV Testing for women with abnormal pap smears.

- USPSTF Reviewed the following studies in their analysis:

Author (Year)	Country	N	Prevalence (%)		
			LSIL	HSIL	CA
Adam (1998)	US (Indigent)	454	55.3	14.5	0.4
Bollen (1997)	Denmark	190	57.8	29.5	0
Herrington (1995)	Britain	167	CIN1=15.0	CIN2=7.2; CIN3=16.8	0
Hillemans (1999)	Germany	247	CIN1=7.3	CIN 2/3=15.4	0.81
Manos (1999)	US	973	12.8	6.7	0.1
Sigurðsson (1997)	Iceland	358	CIN1=16.5	CIN2=15.9; CIN3=36.6	2.0
Sum (1995)	US/CAN	520	31	18.8	1.3

USPSTF Screening Recommendations for Cervical Cancer. Available at: <http://www.ncbi.nlm.nih.gov/books/NBK42834/#A4194>.

HPV Test as Triage Tool for HSIL USPSTF Summary of Evidence

	PCR	Hybrid Capture
Total n	1689	1740
Sensitivity	81	84.6
Specificity	51.3	59.6
Positive Predictive Value	38.5	22.1
Negative Predictive Value	87.7	96.6
Positive Likelihood Ratio	1.7	2.1
Negative Likelihood Ratio	0.4	0.3

USPSTF Screening Recommendations for Cervical Cancer. Available at: <http://www.ncbi.nlm.nih.gov/books/NBK42834/#A4194>.

HPV Test as a Triage Tool Summary

- Good negative predictive value
- Feasible to utilize negative results to:
 - determine interval between Pap test
 - Appropriately refer patients to colposcopy

USPSTF Screening Recommendations for Cervical Cancer. Available at: <http://www.ncbi.nlm.nih.gov/books/NBK42834/#A4194>.

Screening Methods for Cervical Cancer

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Colposcopy

- Allows direct visualization of cervix for purposes of targeted biopsies of abnormal areas

	Acetowhite	Borders	Mosaicism	Vessels
Normal	Pale	Feathered	None	Fine/ None
Low-grade	Shiny gray	Distinct, Jagged	Fine	Fine punctations
High-grade	Dull oyster white	Peeling or rolled edges Internal borders	Coarse	Coarse punctations Large vessels

K Robison and DS Dizon. Dx/Rx Cervical Cancer, 2011 (Jones & Bartlett)

Outline

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- Worldwide Implications

Preventing Cervical Cancer

- Persistent HPV Infection carries risk of transformation
- Risk behavior reduction is key
 - Protective effects of condoms is unknown
- HPV Vaccination is key to prevention
 - Applicable worldwide
 - Addresses disparities in access to screening

	Quadrivalent	Bivalent
Manufacturer	Merck	GlaxoSmithKline
Trade Name	Gardasil®	Cervarix®
HPV-strain VLP	6,11,16,18	16,18
Adjuvant	Aluminum salt	Aluminum salt plus monophosphoryl lipid
Production	Yeast	Recombinant viral infected cells
FDA Approved Indications	Prevention of HPV-associated diseases in all patients, aged 9-26 (incl warts and anal cancer)	Prevention of precancerous lesions of cervix and cervical cancer in girls and women aged 10-25
Schedule	3 injections at 0,2,6m	3 injections at 0,1,6m

K Robison and DS Dizon; DvRx Cervical Cancer, 2011 (Jones & Bartlett)

HPV Efficacy: Quadrivalent Vaccine

Main results of clinical trials

- Villa, 2005 (Lancet Oncol):
 - 90% protection against persistent HPV Infection
 - 100% protection against CIN-1
- Villa, 2006 (Br J Cancer):
 - Subset analysis of 241 patients followed for 5 years showed sustained efficacy
- Brown, 2007 (Abstract):
 - Analysis of 9000 women treated on trials vs. placebo showed 38% reduction in risk of infection by 10 other oncological HPV types (beyond 16/18)
- Giuliano, 2011 (NEJM):
 - 4065 males (16-26), vaccine vs. placebo showed 90% efficacy (per-protocol population)

K Robison and DS Dizon; DvRx Cervical Cancer, 2011 (Jones & Bartlett)

Quadrivalent Vaccine Toxicity

- CDC Report (2009) on post-licensure safety surveillance:
 - Rate of adverse events: 54 per 10,000 doses
 - Prevalence of serious events: 6% (including 32 deaths)
 - Most common events (per 100,000 doses):

Syncopal (8)	HSR (3.1)	Death (0.1)
injection site (7.5)	Urticaria (2.6)	Transverse myelitis (0.04)
Dizziness (6.8)	VTE (0.2)	Pancreatitis (0.04)
Nausea (5)	Guillain-Barre (0.2)	Motor neuron disease (0.009)
Headache (4)	Anaphylaxis (0.1)	

BA Slade, L Leidel, et al. JAMA 2009; 302:750-57.

HPV Prevention: Bivalent Vaccine

- PATRICIA (Papilloma Trial against Cancer In young Adults)
 - n= 18,644 women
 - Enrolled regardless of baseline HPV status
 - 6 or less lifetime partners
 - Randomization was bivalent vaccine vs. HAV
 - At mean follow-up of 35 months:
 - 98% efficacy vs. CIN-2 associated with HPV 16/18
 - Cross-protection vs. HPV 31, 45 observed

K Robison and DS Dizon; DvRx Cervical Cancer, 2011 (Jones & Bartlett)

HPV Vaccination American Cancer Society Recommendations

- Routine vaccine in females ages 11-12
- Females as young as 9 can begin vaccination
- Vaccinate females aged 13-18
- Vaccination of women 19-26 requires informed discussion
 - Less benefit noted in women who averaged 2-4 sexual partners before vaccination
 - Vaccine not tested in women with 4 or more partners
- HPV Vaccination not recommended for women over 26
- Cervical screening is still recommended
- As of 2010: HPV vaccine not recommended for boys or men

HPV Vaccination During Pregnancy

- Initiation of the vaccine series should be delayed until after completion of pregnancy
- If a woman is found to be pregnant after initiating the vaccination series, remaining doses should be delayed until after the pregnancy
- If a vaccine dose has been administered during pregnancy, there is no indication for intervention

MMWR 2007;56(RR-2):1-24. www.cdc.gov/vaccines/pubs/pinkbook/downloads/Slides/HPV11.ppt

Cervical Cancer Screening

- Cervical cancer screening – no change
 - 30% of cervical cancers caused by HPV types not prevented by the quadrivalent HPV vaccine
 - Vaccinated females could subsequently be infected with non-vaccine HPV types
 - Sexually active females could have been infected prior to vaccination
- Providers should educate women about the importance of cervical cancer screening

www.cdc.gov/vaccines/pubs/pinkbook/downloads/Slides/HPV11.ppt

Conclusions

- Cervical cancer can be a devastating disease
 - Best chances of cure when early stage at diagnosis
- The etiology of cervical cancer is viral
 - Excellent chance to prevent
- HPV Vaccination holds the key to eradication of cervical cancer
 - Must be incorporated in to general health prevention in youth
 - Will not eliminate the need for cervical cancer screening
 - Can address worldwide disparities where screening is not feasible

Eradicating cervical cancer in the developing world?

- What is the effect of a single round of HPV testing
 - Indian study involving over 130,000 women
 - HPV Testing compared to cytologic testing and visual assessment
 - HPV Test associated with:
 - 53% reduction in the detection of advanced disease over standard of care
 - 49% improvement in risk of death
 - Reductions were not seen with either cytologic screening or visual inspection

R Sankaranarayanan, et al. *NEJM* 2009; 360:1385-94

HPV Testing plus vaccination: A global partnership

- Partnership developed between the government of the African nation of Rwanda, Quiagen (maker of an HPV screening test) and Merck (manufacturer of the Quadrivalent HPV vaccine)
 - Quiagen will provide free HPV screening kits to women between 35 and 45
 - Merck will donate HPV vaccine to girls 12 to 15 years of age.
 - More than 2 million doses of the HPV vaccine and 250,000 screening tests will be provided in this collaboration.

Questions?

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