

Women's Health Grand Rounds

**Cancer Screening and Prevention:
Eliminating Deaths from Cervical Cancer**

ACOG District II and New York State DOH

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**Cancer Screening and Prevention:
Eliminating Deaths from Cervical Cancer
Speakers**

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**Cancer Screening and Prevention:
Eliminating Deaths from Cervical Cancer
Speakers**

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Obstetricians and Gynecologists
(ACOG) District II/NY**
- **Produced by University at Albany,
School of Public Health**



Disclaimer

- **Dr. Nicholas Montalto serves as a
member of the Speaker's Bureau for
Merck & Co., Inc.**

Learning Objectives

- **Describe the current evidence-based
guidelines on cervical cancer screening**
- **Describe HPV and explain its relationship to
cervical cancer and indications for HPV
testing**
- **Explain the HPV vaccine, including current
recommendations for its uses**

Screening with the Conventional Pap Smear

- Sample collected undergoes cytologic evaluation
- Limitations
 - Screening test, not diagnostic
 - 7-10% of women screened will need further evaluation
 - Low sensitivity, high specificity

Cervical Cytology Screening, ACOG Practice Bulletin No. 45, 2003; 102:417-27.

Sources of Error with the Conventional Pap Smear

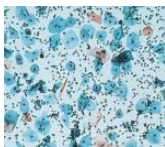
- Sampling / preparation errors¹
 - Cells not collected on sampling device
 - Collected cells not transferred to slide
 - Poorly preserved cells
- Screening / interpreting errors^{2,3}
 - Abnormal cells missed by cytologist
 - Cells incorrectly classified

2/3 of false negatives

1/3 of false negatives

1. Hutchinson ML, et al. Am J Clin Pathol. 1994; 101:215-219.
 2. Linder J, et al. Arch Pathol Lab Med. 1998; 122: 139-144.
 3. Agency for Health Care Policy and Research. Evaluation of Cervical Cytology. 1999.

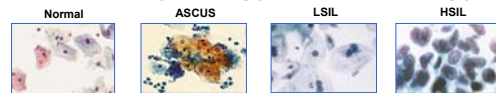
Thin-Layer Preparations



- Reduce Sampling Errors
 - Virtually all of the sample is collected into the vial
 - Randomized, representative sample
- Reduce Screening Errors
 - Thin, uniform layer of cells
 - "Satisfactory, but limited" specimens greatly reduced
 - Screening errors reduced by 50%

Linder J, et al. Arch Pathol Lab Med. 1998; 122: 139-144.

Cervical Cytology Terminology



- Atypical squamous cells (ASC)
 - Atypical squamous cells of undetermined significance (ASC-US)
 - Atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesions (ASC-H)
- Squamous intraepithelial lesions (SIL)
 - Low-grade SIL (LSIL): Mild dysplasia, cervical intraepithelial neoplasia 1 (CIN 1)
 - High-grade SIL (HSIL): Moderate and severe dysplasia (CIN 2/3) carcinoma in situ (CIS)
- Atypical glandular cells (AGC)

Cervical Cancer Screening Guidelines

How often:

- Adults
 - Annually with conventional paps and every 2 years with liquid-based cytology
 - ≥30 with 3 consecutive negatives may change to every 2-3 years
 - Guidance by HPV status
- Adolescents
 - First screen 3 years after onset of sexual intercourse or at age 21

*Exclusions: DES exposure, Immunocompromised, HIV
 Cervical Cytology Screening, ACOG Practice Bulletin No. 45, 2003; 102:417-27.

Cervical Cancer Screening Guidelines

When To Stop:

- Women >70 years with:
 - At least 3 consecutive documented, satisfactory negative smears¹
 - No abnormal/positive cytology within past ten years¹
- After hysterectomy
 - If hysterectomy performed for benign disease and cervix was removed²
 - Negative history of abnormal paps²

*Exclusions: DES exposure, Immunocompromised, HIV, newly positive high-risk HPV DNA test

1. American Cancer Society. Cancer facts & figures 2003. 2. Cervical Cytology Screening, ACOG Practice Bulletin No. 45, 2003; 102:417-27.

High-Risk HPV Testing ACOG Guidelines

Two Indications:

- Primary screening after age 30
 - If both Pap and High-Risk HPV test negative
 - Re-screen no more frequently than every 3 years
- Triage of minimally abnormal Paps after age 20
 - ASC-US
 - Only need to do colposcopy if High-Risk HPV +

Cervical Cytology Screening, ACOG Practice Bulletin No. 45, 2003; 102:417-27.

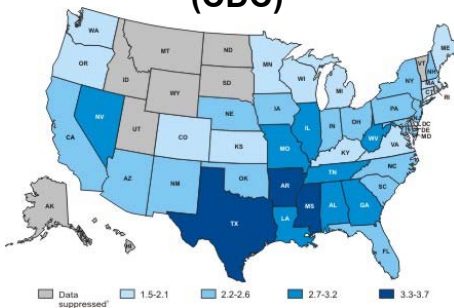
New York State

- **946 cases of cervical cancer occur in New York State each year.**
- **288 deaths annually, with a mortality rate of 2.6 cases per 100,000 person.**

NSYDOH, Vital Statistics, 2000-2004 data



Cervical Cancer Mortality Rates* by State, 2004 (CDC)



Nationally

- It is predicted that there will be **11,070** new cases of invasive cervical cancer in the United States in 2008.
- About **3,870** women will die from cervical cancer this year.

American Cancer Society, 2008



Worldwide

- **83%** of the world's new cases of cervical cancer occur in developing countries.
- **85%** of all cervical cancer deaths occur in developing countries.



Alliance for Cervical Cancer, 2005

HPV & Cervical Cancer

- HPV is the underlying cause of cervical cancer
 - NIH Consensus Conference on Cervical Cancer, 1996
 - World Health Organization/European Research Organization on Genital Infection and Neoplasia, 1996
 - Journal of the National Cancer Institute
 - Schiffman, et al., 1993
 - France, et al., 1995
 - Bosch, et al., 1995
- HPV is present in over 99.7% of cervical cancers
 - ACOG Practice Bulletin, 2005

Human Papillomavirus (HPV)



- Over 100 types identified²
 - 30–40 anogenital^{2,3}
 - 15-20 oncogenic types^{2,3}
 - 30-35 types sexually transmitted
- Disease Burden
 - 20,000,000 current cases in US⁶
 - 6,200,000 new annual cases⁵
 - 80% of women will have acquired HPV infection by age 50⁵
 - 50% of college students are infected⁴

1. Howley PM. In: Fields BN, Knipe DM, Howley PM, eds. *Fields Virology*. 4th ed. Philadelphia, Pa: Lippincott-Raven; 2001:2197–2229. Picture reprinted with the permission of Lippincott-Raven.
 2. Schiffman M, Castle PE. *Arch Pathol Lab Med*. 2003;127:930–934.
 3. Wiley DJ, Douglas J, Beutner K, et al. *Clin Infect Dis*. 2002;35(suppl 2):S210–S224.
 4. Winer RL et al. *Am J Epidemiol*. 2003; 157:218–226.
 5. Centers for Disease Control and Prevention. Rockville, Md. CDC National Prevention Information Network; 2004.
 6. Cates W Jr, and the American Social Health Association Panel. *Sex Transm Dis*. 1999;26(suppl):S2–S7.

Common HPV Types Associated With Benign and Malignant Disease

HPV Types	Manifestations
Low-Risk HPV 6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81	Benign low-grade cervical changes Condylomata acuminata (Genital warts)
High-Risk HPV 16, 18, -31, -33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82	Low-grade cervical changes High-grade cervical changes Cervical cancer Anogenital and other cancers

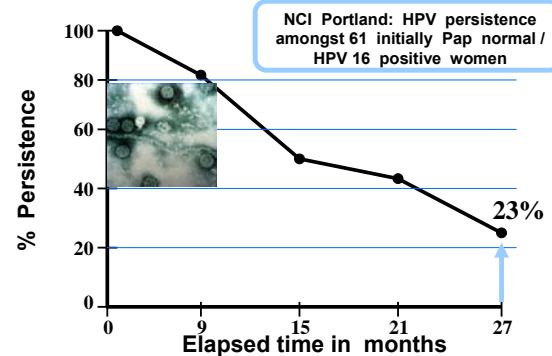
1. Cox. *Baillière's Clin Obstet Gynaecol*. 1995;9:1.
 2. Munoz et al. *N Engl J Med*. 2003;348:518.

Natural History of HPV Infections

- HPV is sexually transmitted
 - Asymptomatic
 - No treatment for HPV infection
 - Cervical changes and warts CAN be treated
 - Transient or persistent
- Cofactors for cervical carcinogenesis
 - Smoking
 - HIV infection and other host immune factors
 - Parity
 - Oral contraceptive use

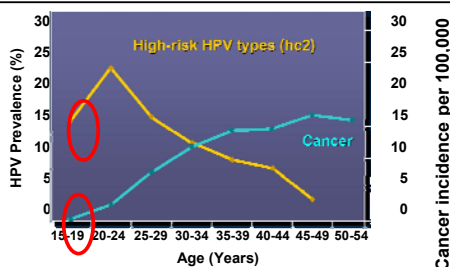
Human Papillomavirus. ACOG Practice Bulletin No. 61. 2005; 105: 905-18. Ferris et al. *Modern Colposcopy*, 2004

Most HPV Infections are Transient



Schiffman M ASCCP 2002 Biennial Orlando, FL.

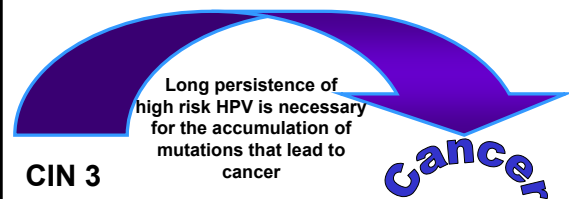
HPV Prevalence and Cervical Cancer Incidence by Age^{1,2}



1. Sellors et al. *CMAJ*. 2000;163:503.
 2. Ries et al. Surveillance, Epidemiology and End Results (SEER) Cancer Stats NCI, 1973-1997. 2000.

HPV Infections: Summary

- Most will acquire HPV at some time
- Most will clear HPV, but some do not
- Persistence of low-risk HPV can lead to anogenital warts
- Persistence of high-risk HPV can lead to pre-cancer



Case # 1

45 year old female

- Asymptomatic
- Routine pap results ASC-US

What should you do?



Case # 1, continued

- Repeat pap at 12 months reveals ASC-US
- Do you perform an HPV test again?

What should you do?



2006 ASCCP Guidelines: Special Populations

Women 20 years and under

- Do NOT perform reflex HPV testing for ASC-US or LSIL Pap results

Pregnant women

- Treatment should be done only for invasive cancer
- Do NOT perform endocervical curettage
- Colposcopic referral to those experienced with pregnancy evaluation

Postmenopausal women

- For LSIL result, reflex HPV DNA testing is acceptable to triage for colposcopy

Case # 2

35 year old female

- Asymptomatic
- Pap reveals AGC

What should you do?

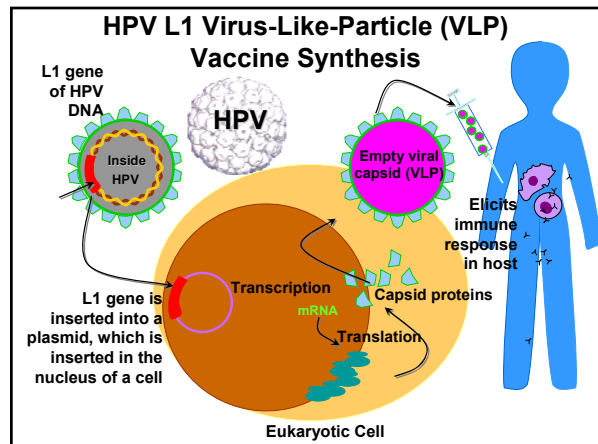


HPV Vaccine

Gardasil® (Merck)

- Quadrivalent vaccine against types 16, 18, 6, 11
- FDA approved for use in females 9-26 years of age
- Prophylactic, not therapeutic
- Virus-like particles (VLP)
- Highly effective
- Safe, few serious adverse side effects
- Requires 3 injections
- Expensive (\$360 + administrative fees)

Smith, RA et al. Cancer. 2003;53(1): 27-43.



Prevention of HPV16/18-Related Precancerous Cervical Lesions (CIN2/3) in a Susceptible Population

HPV16 and/or HPV18 negative at enrollment
Mean 25 months of follow-up (starting 1 month postdose 1)

Endpoint	Vaccine Cases† (N=9,342)	Placebo Cases† (N=9,400)	Vaccine Efficacy (95% CI)
HPV 16/18-related CIN 2/3 or AIS	1	81	99% (93, 100)
HPV 16/18-related CIN 2	1	55	98%
HPV 16/18-related CIN 3/AIS	0	52	100%

† Subjects are counted once per row. Subjects may be counted in >1 row.

GARDASIL® (Quadrivalent Human Papillomavirus [HPV Types 6, 11, 16, 18] Recombinant Vaccine)

General Population Impact: GARDASIL Reduced HPV 16- and 18-related CIN 2/3 or AIS

HPV 16- or 18-Related CIN 2/3 or AIS	N	GARDASIL or HPV 16 L1 VLP Cases	N	Placebo Cases	% Reduction	95% CI
Prophylactic Efficacy*	9,342	1	9,400	81	98.8%	93–100
HPV 16 and/or HPV 18 Positive at Day 1	—	121	—	120	—	—
General Population Impact†	9,831	122	9,896	201	39.0%	23–52

*Includes all subjects who received at least 1 vaccination and who were naive (PCR (-) and sero (-)) to HPV 6, 11, 16, and/or 18 at Day 1. Case counting started at 1 month Postdose 1.
†Includes all subjects who received at least 1 vaccination (regardless of baseline HPV status at Day 1). Case counting started at 1 month Postdose 1.

Note: Table does not include disease due to nonvaccine HPV types.

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HPV Vaccine Safety

- Over 9 million doses distributed
- Nearly 95% are non-serious
 - Vomiting/syncope/fever/nausea/pain at injection site
- Serious Adverse Events reported rarely
 - No concerning pattern among serious events
 - Proportion of serious reports less than half the overall average for VAERS
- Many events reported have high baseline rates in absence of vaccination (e.g. syncope)
- Reported deaths do not appear to be causally related to vaccination

VAERS Report, September 30, 2007

Vaccine Specifics

- **Dosage Schedule**
 - 3 separate 0.5-mL doses at 0, 2 months, 6 months
 - Evidence suggests adequate immune response if all 3 doses given within 12 months
- **Ordering**
 - Through Merck
 - www.MerckVaccines.com
 - 1-877-VAX-MERCK
 - Vaccine Patient Assistance Program
 - Vaccines for Children Program
 - http://www.cdc.gov/nip/vfc/provider/provider_home.htm
- **Storage**
 - Refrigerated at 2-8°C (36-46°F)
- **Consent**
 - Currently in NYS, minors need parental consent
- **Adverse event reporting**
 - <http://vaers.hhs.gov/>

Human Papillomavirus Vaccination. ACOG Committee Opinion No. 344. 2006; 108: 699-705.

Resources

ACOG District II/NY Website:
<http://www.acogny.org>

Centers for Disease Control and Prevention (CDC) <http://cdc.gov/>

New York State Department of Health
<http://www.health.state.ny.us/>

Evaluations

Please fill out your evaluation and post-test online:

<http://www.albany.edu/sph/coned/whgracogcancer.htm>

Continuing education credits are available.

Thank You!