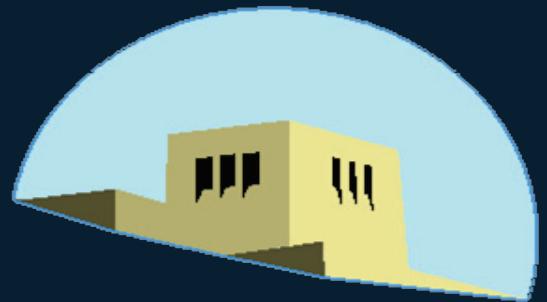


What's New in Prevention of Cervical Cancer: 2011

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What's new in cervical
cancer prevention???

Photo: A. Waxman



This field is evolving so rapidly,
the question has to be asked
“What's new since when?”



Photo: A. Waxman

- In the past 30 years the incidence and mortality from cervical cancer in AI / ANs has declined dramatically.
- In the last 20 years HPV was identified as the cause of cervical cancer.
- Over the last 15 years, most of us have switched from the conventional Pap smear to a liquid-based Pap test.
- In the last 10 years, we've added HPV DNA testing and type 16/18 genotyping to our screening armamentarium.
- In the past 13 years thanks to the Bethesda Conferences, Pap terminology has been standardized - 3 times
 - And ASCCP's guidelines for management of abnormal results were developed and revised.
- Over the past 8 years screening guidelines have changed twice, including a more conservative approach to young women.
- In the last 5 years we've gotten a vaccine against the two HPV types that cause 70% of cervical cancer.
- In the past 5 years laboratories have added computer driven automation to cytology screening
- In the past year - a second HPV vaccine and a third HPV DNA test.

Objectives

- Review the most recent epidemiology on cervical cancer in Native Americans.
- Discuss the HPV vaccines- benefits, risks
- List new recommendations for cervical cancer screening
- Discuss the role of HPV DNA testing in screening for cervical cancer.

- In the U.S. there are about 11,000 new cases of cervical cancer in American women each year.
 - And about 4,000 cervical cancer deaths.
- 60% of women who get cervical cancer haven't had a Pap test within the past 5 years.
- Worldwide cervical cancer is the second most common cancer among women, the single largest cause of years of life lost to cancer in developing countries.
 - 493,000 new cases annually worldwide
 - 274,000 deaths

How are we doing at preventing cervical cancer in Indian Country?



Photo: A. Waxman

- 1978-81: Native Americans had the highest incidence of cervical cancer among U.S. ethnic/racial groups
 - 22.6 / 100,000
- 2000-04: Native Americans have the lowest incidence of cervical cancer among U.S. ethnic/racial groups
 - 6.6 / 100,000

Cervical Cancer Incidence Rates by Race 2000-2004

Espey DK, et.al. Cancer 2007;110:2119-2152

Cervical Cancer in Indian Country: Where we've come from; Where we are

- Current data is not quite so good for American Indians and Alaska Natives living in on or near federally recognized tribal lands
 - Cervical cancer incidence: 9.4 / 100,000

Incidence for Contract Health Service Delivery Areas: Counties with or adjacent to tribal lands.

American Indian/ Alaska Native Cervical Cancer Incidence by Residence 1998-2001

Bernard et.al. Obstet Gynecol 2007;110:681-686

Incidence of Cervical Cancer

American Indian / Alaska Native: 1999-2004

Becker et.al. Cancer 2008;13(5 suppl):1234-43



As of Dec. 2008, 55% of 13-17 y.o. AI/AN girls had received at least the first HPV immunization injection.

This compares with 44.3% of U.S. all races 13-17 y.o. girls in 2009.

Unfortunately only 18% of AI/An girls had completed all 3 injections.

How does the HPV Vaccine work?

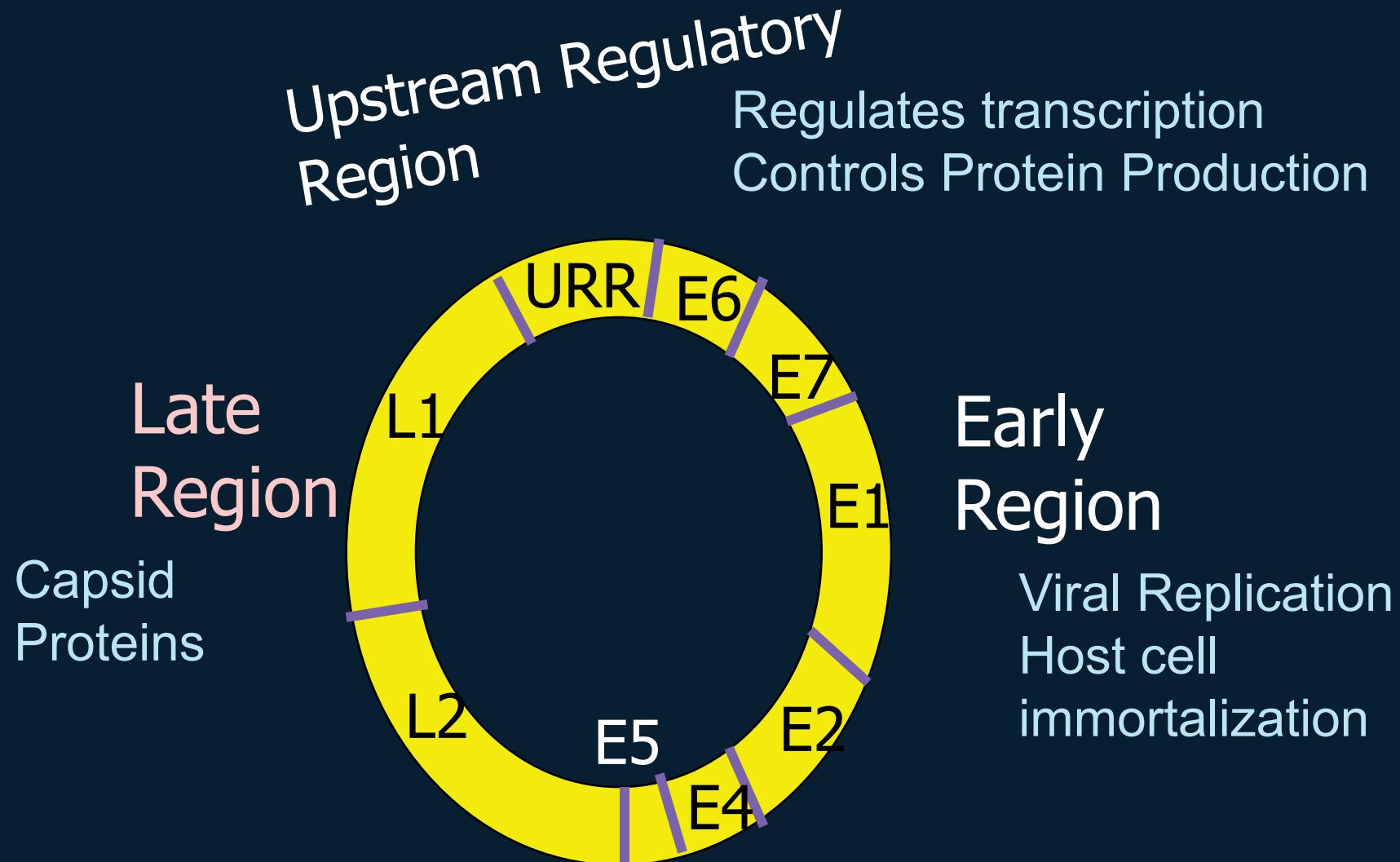


Photo: A. Waxman

Human Papillomavirus

- Double stranded DNA virus
- Capsid - 72 icosahedral capsomeres
- 15 types known to produce cancer (3 others suspected)
 - 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82
 - Types 16 and 18 responsible for 2/3 to ¾ of cervical cancers worldwide
 - Type 16 causes almost half of invasive cancers.
 - Types 18, 31, 33, 52, and 58 together account for over one third of cancers.

Organization of HPV Genome



Primary Prevention: The HPV Vaccine

Studies in 1990s showed that Canine Oral Papillomavirus could be prevented using capsid proteins recombined into virus like particles (VLP)

FDA Approved HPV Vaccines

- Quadrivalent vaccine: HPV 6,11,16,18
 - Merck markets under name Gardasil
 - Aluminum hydroxyphosphate sulfate adjuvant
 - FDA approved, June 2006 for females aged 9-26
 - Approved October 16, 2009 for males aged 9-26 to prevent external genital warts caused by HPV 6/11
- Bivalent vaccine: HPV 16,18
 - Glaxo Smith Kline markets as Cervarix
 - ASO4 adjuvant (Aluminum hydroxide and 3-O-desacyl-4'-monophosphoryl lipid A)
 - FDA approved October 16, 2009 for females aged 10-25

How effective is the HPV Vaccine?



Photo: A. Waxman

HPV Vaccines stimulate a robust and long lasting immune response

- Phase II HPV 16 L1 vaccine study
- Antibody titers start to increase immediately after first dose
 - By 2 months titers reach levels induced by natural HPV infection
 - After third dose, levels rise to almost 2 orders of magnitude higher than natural immunity
- Remain almost 10 fold higher than natural immunity after 42 months
 - Remain elevated for at least 5-6 years

“Per-protocol” or “Intention-to-treat”

Per-protocol

- Adhere strictly to study protocol
 - Receive all three doses
- Free from endpoint diseases or infection with covered HPV types from enrollment through vaccination period
- Reflects vaccine efficacy under ideal conditions

Intention-to-treat

- May or may not adhere to all aspects of protocol
 - Receive at least one dose
- May have been infected with one or more covered HPV types and/ or have endpoint disease related to covered HPV type at enrollment or during vaccination period
- Reflects vaccine efficacy under “real world” conditions

Different endpoints used in each vaccine’s intention-to-treat analysis

Per-protocol Efficacy

Efficacy against disease associated with vaccine included HPV types (16/18 or 16/18/6/11)

- Bivalent vaccine (Mean f/u 34.9 months)
 - Efficacy against CIN 2+ **98.1%** (CI 88.4-100)
 - cases rare: 1 in vaccine group / 53 in control
 - Efficacy against CIN 3+ **100%** (CI 36.4-100)
 - 0 cases in vaccine group / 8 in control
- Quadrivalent vaccine (Mean f/u 42 months)
 - Efficacy against CIN 3,2, AIS **98.2%** (CI 93.3– 99.8)
 - 2 cases vaccine group / 110 in control

*Kjaer et al. Cancer Prev Res 2009;2 (10) October 2009
Paavonen J et.al. Lancet July 7, 2009.*

Intention-to-Treat Efficacy

Efficacy against disease associated with vaccine included HPV types (16/18 or 16/18/6/11)

- Quadrivalent Vaccine
 - Included those who may have been infected with vaccine included HPV types at onset of study
 - Efficacy against CIN 3,2, AIS **51.5%** (CI 40.6– 60.6)
 - 142 cases vaccine group / 293 cases in control
- Bivalent Vaccine
 - All had prior exposure to HPV 16 and/or 18
 - Included those with abnormal cytology
 - **No difference** between vaccine and control group

Intention-to-Treat Efficacy

Efficacy against disease associated with *any* HPV type

- Bivalent Vaccine
 - Efficacy against CIN 2+ **30.4%** (CI 16.4-42.1)
- Quadrivalent Vaccine
 - Efficacy against CIN 2+, AIS **17%** (CI 1-31)

Paavonen J et.al. Lancet July 7, 2009. FUTURE II Study Group NEJM 2007;356:1928-43

Intention-to-Treat Efficacy Acquisition of New Lesions Over Time

- In the first one to two years after immunization, women in the immunized and control groups acquired new CIN 2+ lesions at similar rates.
 - Reflects expression of viral infection already present
- Subsequently, new disease was less common in the immunized group.
 - May reflect protection against vaccine included viral types not present at time of immunization
- This phenomenon was seen in both bivalent and quadrivalent vaccine studies

So who should get the HPV vaccine?

Clearly, the HPV vaccine is most effective before a woman has been exposed to one of the covered HPV types.

This means your best bet is to immunize before the onset of sexual activity.

When do young women become sexually active?

- 27% of 9th grade girls (age 14-15) admit to having have had sexual intercourse
 - 5.5% have had sex with four or more partners
 - 4.9% had first intercourse before age 13

So who should get the HPV vaccine?

FDA approved for males and females aged 9-26

ACIP and ACOG recommend vaccinating 11-12 year old girls.
If the vaccine was not given at that age, a “catch-up” immunization may be given to girls/women aged 13-26.

Adverse Events Reported to FDA

Quadrivalent Vaccine: June 1, 2006 – Dec. 31, 2008

Slade BA et al JAMA 2009;302:750-757

- Two complications significantly more common than other vaccines
 - Syncope.
 - Reported rate: 8.2 events / 100,000 distributed doses
(4.8 X more common in girls <18 y.o.)
 - Venous thromboembolic events
 - Reported rate: 0.2 events / 100,000 distributed doses
- Other adverse events reported (rates not more common than other vaccines)
 - Local reaction, dizziness, nausea, headache, allergic reaction
 - Serious events: Guillain Barre, anaphylaxis, death

HPV Vaccine in Pregnancy

- Reports from 4037 pregnancies in phase III clinical trials of quadrivalent vaccine
- No significant differences between vaccine and placebo groups with regard to
 - Live births
 - Spontaneous abortions
 - Late fetal deaths
 - Congenital anomalies
- Classified Category B by FDA
- Lactating women can receive quadrivalent HPV Vaccine per ACIP

*Garland SM et.al. Obstet Gynecol 2009;114:1179-88
MMWR March 23, 2007 / 56(RR02);1-24*

What's new in screening for cervical cancer and management of abnormal results?

- ACOG Guidelines revised and published December 2009
- ASCCP published updated guidelines for managing women with abnormal Pap tests and biopsy results in 2007



Photo: A. Waxman

There's a new emphasis on taking a conservative approach to the screening and subsequent management of teens and young women.



Photo: A. Waxman

Cervical Cytology Screening

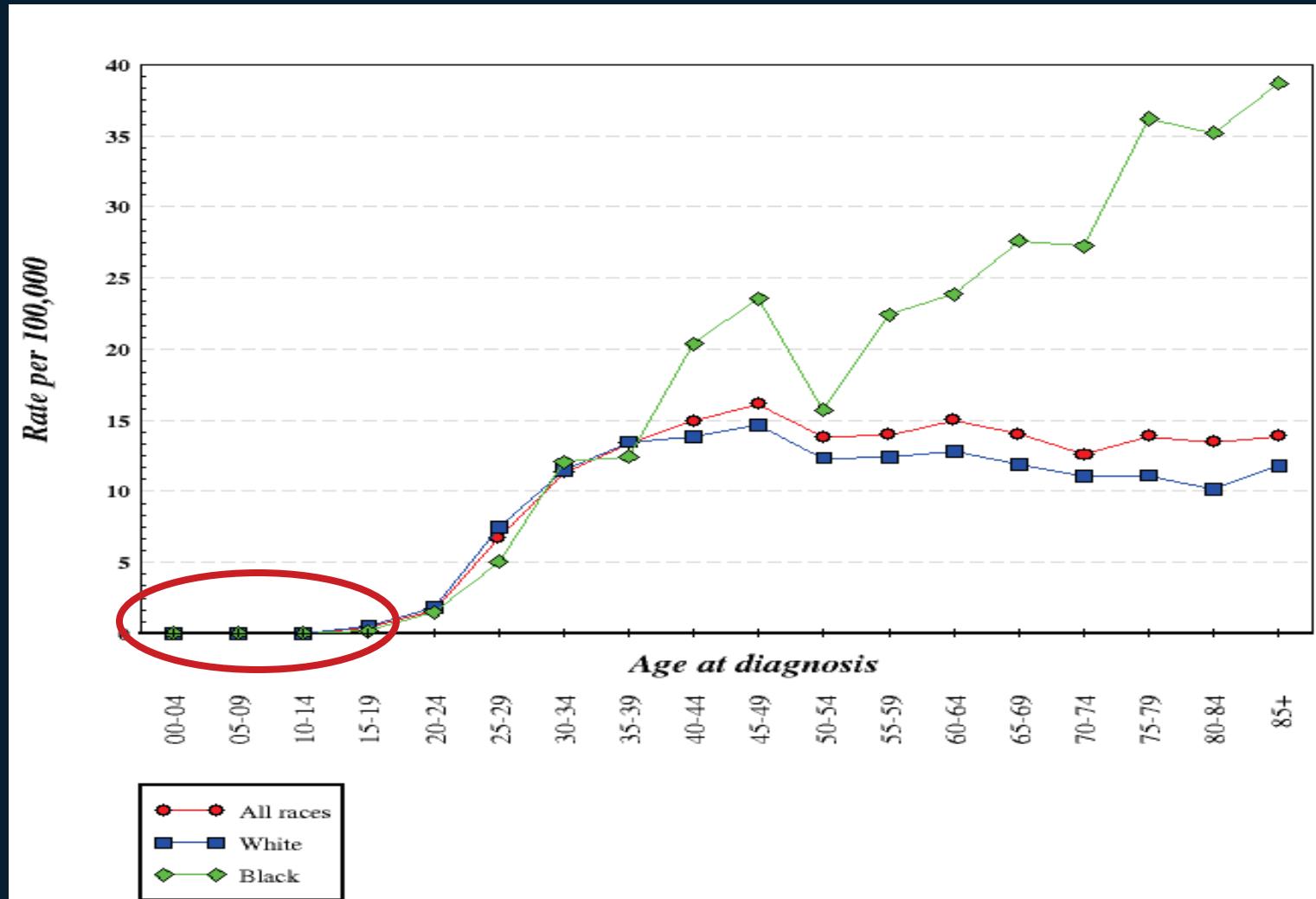
ACOG Practice Bulletin #109

Summary of Recommendations

- Begin cervical cancer screening at age 21
 - Avoid screening before age 21.
 - “...earlier screening may lead to unnecessary and harmful evaluation and treatment in women at very low risk of cancer.”

Based on good and consistent scientific evidence - Level A

Invasive Cervical Cancer is Exceedingly Rare in Adolescents



Invasive Cervical Cancer in Adolescents (Age <21)

- 0.1% of cervical cancers in U.S.
- Rate ~1/ 1,000,000 adolescents
- Ave 14 cases per year in 15-19 year olds.
 - Too rare to report under age 15
 - Rate unchanged between 1973-77 and 1998-2006
 - Recommendation to start screening at age 18 or with onset of intercourse made in 1980s

*Moscicki, Cox, et al J Lower Genital Tract Dis 2010;14:74
(Data from SEER and CDC)*

Rate of Progression, CIN 3 to Cancer

Moscicki, Cox, et al J Lower Genital Tract Dis 2010;14:73-80

- Increases with age
 - Age 80: 10% per year
 - Age 20-24: 0.5% per year
 - Adolescents: negligible

What are the risks in screening teenagers?

- Adverse effects of overdiagnosis and unnecessary treatment
 - Unnecessary treatment of dysplasia associated with increased risk of PPROM and premature birth in future pregnancies.
 - Psychological harm including sexual dysfunction with abnormal Pap results.

Obstetric Outcomes after LEEP: Results of two meta-analyses

- Significant increase in
 - Late preterm births (>32 / 34 wks)
 - pPROM
 - Low birth weight infants
- No significant increase in
 - Preterm births <32/34 weeks
 - Cesarean section
 - NICU admissions
 - Perinatal mortality

M Kyrgiou, et al. Lancet 2006;367:489-498
M Arbyn et.al. BMJ 2008;337: a1284

Cervical Cytology Screening

ACOG Practice Bulletin #109 Summary of Recommendations

- Avoid screening before age 21”
 - “...may lead to unnecessary and harmful evaluation and treatment in women at very low risk of cancer.”
- *Critical that sexually active adolescents be counseled and tested for STDs and counseled regarding sex and contraception.*
 - “...may be carried out without cervical cytology screening and in the asymptomatic patient, without the use of a speculum.”

Based on limited and inconsistent scientific evidence - Level B

But what if she already had a Pap and it was abnormal?

- Colposcopy is not indicated with an initial Pap result of ASC-US or LSIL in a woman under 21.
 - Follow with cytology only.
(without Reflex HPV)
- Most adolescents and young women with CIN1 or 2 on biopsy should be managed without treatment.

It's not really new, but the
"annual" Pap smear is dead!



Photo: A. Waxman

Cervical Cytology Screening

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Summary of Recommendations

- Screening recommended every 2 years between age 21 and 29
- Interval may be extended to every three years aged 30 and older
 - Provided
 - 3 consecutive negatives
 - No history of CIN 2 or 3
 - HIV negative, not immunocompromised
 - Not DES exposed in utero

Based on good and consistent scientific evidence - Level A

How much protection do we lose by not doing Pap tests every year?

- Percentage reduction in rate of invasive cervical cancer in cohort of women aged 35 - 64 with different frequencies of screening
 - Assumes at least negative Pap prior to age 35
 - Next Pap 1 yr: 93.5%
 - 30 Paps required over 30 years
 - Next Pap 2 yrs: 92.5%
 - 15 Paps required over 30 years
 - Next Pap 3 yrs: 90.8%
 - 10 Paps required over 30 years
 - Next Pap 5 yrs: 83.6%
 - 8 Paps required over 30 years

Are we missing cancers by not screening every year?

- Markov model based on NBCCEDP data
- Assumed ≥ 3 prior consecutive negative Paps
- Cancers prevented by doing Pap annually instead of every 3 years
 - Age 30 – 44: 3 / 100,000 women
 - Age 45 – 59: 1 / 100,000 women
- Additional tests needed to find each incremental cancer
 - Age 30 – 44: 69,665 Paps plus 3,861 colpos
 - Age 45-59: 209,324 Paps plus 11,502 colpos

Sawaya et.al. NEJM 2003;349:1501-9

What about the
newer lab
technologies;
liquid Paps, Image
guided cytology,
HPV testing?



Photo: A. Waxman

Cervical Cytology Screening

ACOG Practice Bulletin #109

Summary of Recommendations

- Both liquid-based and conventional methods of cervical cytology are acceptable.

Based on good and consistent scientific evidence - Level A

Meta-analysis Comparing Liquid-based and Conventional Pap Tests

Arbyn et al Obstet Gynecol 2008 111:167-77

- Eight studies mostly from colposcopy clinics where all cases were subjected to gold standard of colposcopy +/- biopsy. One large screening RCT with colposcopy of test positive patients.
- Cytology threshold ASC-US+ to detect histologic CIN 2 +

	<u>Sens.</u>	<u>Spec.</u>
Liquid-based	90.4 (82.5-95.0)	64.6 (50.1-76.8)
Conventional	88.2 (80.2-93.2)	71.3 (58.3-81.6)

	<u>Relative Sens.</u>	<u>Relative Spec.</u>
Liquid/conventional	1.03 (0.97-1.09)	0.91 (0.84-0.98)

Computer-Assisted Screening



Computer-aided Imaging: Focuses Slide Review

- Image processor identifies 22 microscopic fields
- Cytotechnologist reviews the 22 fields (TIS) with an automated review scope
 - If all 22 are judged normal: “No Intraepithelial Lesion”
 - If any are judged abnormal: full slide screening is done for diagnosis

Both FDA approved systems based on similar principles

Computer Assisted Imaging

- Combines advantage of machine – tirelessly locating rare events...with the interpretive advantage of humans
 - Improved screening productivity
 - Over 150 slides per day
 - Manufacturer claims increased sensitivity for ASC-US+ of 6.4%, specificity increased by 0.2%
- FDA approval:
 - Hologic (Cytac) ThinPrep Imaging System- June 2003
 - B-D (Tripath) FocalPoint GS Imaging System- December 2008

Won't making
the Pap test
more sensitive
help us
eradicate
cervical cancer?



Photo: A. Waxman

Who gets cervical cancer?

- Estimated annual contributions to squamous cervical cancer screening failures in the U.S.

	<u>%</u>	<u>No. of women</u>
Never screened	50	6,100
>5 yrs since screened	10	1,210
Errors in follow up	10	1,210
Errors in sampling or interpretation	30	3,630
Total	100	12,200

Shouldn't we
be doing HPV
DNA testing
on everybody?



Photo: A. Waxman

Cervical Cytology Screening

ACOG Practice Bulletin #109

Summary of Recommendations

- Co-testing with cytology plus HPV DNA testing is an appropriate screening test for women older than 30 years.
- Any low-risk woman aged 30 or older who tests negative on both cytology and HPV DNA should be rescreened no sooner than three years

Based on good and consistent scientific evidence - Level A

Cervical Cytology Screening

ACOG Practice Bulletin #109

Summary of Recommendations

- Co-testing with cytology plus HPV DNA testing is an *appropriate* screening test for women older than 30 years.
- Any low-risk woman aged 30 or older who tests negative on both cytology and HPV DNA should be rescreened no sooner than three years

Based on good and consistent scientific evidence - Level A



So that's some of
what's new with
cervical cancer
prevention.

Photo: A. Waxman

In the next webex, we'll talk more about managing adolescents and screening with HPV and Paps together.



Photo: A. Waxman