Screening and Prevention of Cervical Cancer

What's new in cervical cancer prevention?

Background

- Over the past 30 years, the AI/AN mortality from cervical cancer has declined dramatically;
- In the past 20 years, HPV was identified as the cause of cervical cancer;
- Over the past 15 years, most clinicians have switched from the Pap smear to a liquid-based Pap test

Background

- In the past 10 years, we've added HPV DNA testing and more recently type 16/18 genotyping to our screening regimen;
- In the past 13 years, Pap terminology has been standardized – 3 times;
- Over the past 10 years, screening guidelines have changed twice
  - with a more conservative approach to young women.
  - and development and revision of ASCCP's guidelines for management of abnormal results.

Background

- In the past 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 became available.

Objectives

- Review the most recent epidemiology on cervical cancer in AI/AN women;
- List new recommendations for cervical cancer screening;
- Discuss HPV vaccination;
- Discuss the role of HPV DNA testing in screening for cervical cancer.

In the U.S., there are about 12,000 new cases of cervical cancer in American women each year, and about 4,000 cervical cancer deaths.

Worldwide, cervical cancer is the second most common cancer among women, and the single largest cause of years of life lost to cancer in developing countries with 493,000 new cervical cancer cases annually and 274,000 cervical cancer deaths.

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

- 1978-1981: AI/ANs had the highest incidence of cervical cancer among all U.S. ethnic/racial groups - 22.6/100,000.
- 2000-2004: AI/ANs have the lowest incidence of cervical cancer among all U.S. ethnic/racial groups – 6.6/100,000.

Cervical Cancer in Indian Country: Where we were; where we are now

- We are not where we were in 2004:
  - The incidence of cervical cancer for AI/AN women is now 9.4/100,000.

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

Who Gets Cervical Cancer?

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

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

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What Causes Cervical Cancer?

- Human Pappilomavirus; a double stranded DNA virus
- Types 16 and 18 responsible for 2/3 to 3/4 of cervical cancers worldwide
- Types 31, 33, 52, 58 together account for over 1/3 of cancers.

How can we prevent HPV? FDA Approved HPV Vaccines

- Quadravalent vaccine: HPV 6, 11, 16, 18
  - Merrick markets under name Guadasil
  - FDA approved June, 2006 for females aged 9-25
  - Approved October 16, 2009 for males aged 9-26 to prevent external genital warts
- Bivalent vaccine: HPV 16, 18
  - Glaxo Smith Kline markets as Cervarix
  - FDA approved October 2009 for females aged 10-25

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 3rd 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

When is the HPV vaccine most effective?

- Before a woman has been exposed to one of the covered HPV types.
- Therefore, it's best 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 had sexual intercourse
  - 5.5% have had sex with four or more partners
- 4.9% had first intercourse before age 13

CDC Youth Risk Behavior Surveillance, United States 2007, MMWR. 2008;57 No.SS-4

So who should get the HPV vaccine?

- FDA approved for males & females aged 9-26
- ACIP (CDC's Committee on Immunization Practices) 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 13-16.

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
MWR March 23, 2007 / 56(RRO2);1-24

How well are we immunizing our girls and our young women?

- As of December 2008, 55% of 13-17 yr old AI/AN girls had received at least the first HPV immunization;
- This compares with 44.3% of U.S. all races 13-17 yr old girls in 2009;
- Only 18% had completed all 3 immunization injections.

Data from IHS Immunization Program, 2009, MMWR; August 20, 2010/59(32);1018-1023

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

- ACOG Guidelines revised and published December 2009.

- The ASCCP published updated guidelines for managing women with abnormal Pap tests and biopsy results in 2007

American Journal of Obstetrics and Gynecology (2007;197(4):346-355).

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

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 Extremely Rare in Adolescents (Age <21)

- 0.1% of cervical cancers in the U.S.
- Rate is around 1/1,000,000 adolescents
- Average of 14 cases per year in 15-19 yr olds
  - Too rare to report under age 15
  - Rate unchanged between 1973-'77 and 1998-'06
    - The recommendation to start screening at age 18 or with onset of intercourse was made in the '80's.

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

What are the risks in screening teenagers?

- Adverse effects of over diagnosis and unnecessary treatment (esp. LEEP)
  - 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

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."
- Sexually active adolescents younger than 21 yrs should be counseled and tested for STIs and counseled regarding safe sex and contraception.
  - "…may be carried out without cervical cytology screening and in the asymptomatic patient, without the use of a speculum."

Based on good and consistent scientific evidence – Level A

Cervical Cytology Screening ACOG Practice Bulletin #109 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 that:
  - 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

What about liquid-based Paps?

Cervical Cytology Screening ACOG Practice Bulletin #109 Summary of Recommendations

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

Meta-analysis Comparing Liquid-based and Conventional Pap Tests

- 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.

Liquid-based:

sensitivity 90.4 (82.5-95.0) specificity 64.6(50.1-76.8)

Conventional

sensitivity 88.2 (80.2-93.2) specificity 71.3 (58.3-81.6)

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

Who gets cervical cancer?

- Estimated annual contributions to squamous cervical caner screening failures (+ Paps) in the U.S.

	%	# of women
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

Sawaya Obstet Gynecol 1999 / ACS facts and figures 20120

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

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 in no sooner than three years.

Based on good and consistent scientific evidence – Level A

A negative HPV DNA test offers better protection after 6 years than a negative Pap does after 3 years.

- Joint European Cohort Study compared HPV testing with conventional Pap in 6 countries
- N=24,295
- The rate of CIN 3+ after baseline negative test was 0.51% three years after a PAP test, and 0.27% six years after HPV testing.

Dillner, J. et.al. BMJ 2008;337:a1754

Thank you for everything you do to prevent cervical cancer!