

## **Update: Latest Pap Test Guidelines and HPV testing**

Sarah Feldman MD MPH  
Director Pap Smear Center  
Brigham & Women's Hospital  
Dana Farber Cancer Institute  
Harvard Medical School

## **Financial Disclosures**

- none

## Objectives

- Be familiar with new screening recommendations and management guidelines
- Understand the data behind the guidelines
- Learn how HPV testing may be used

## What is unique about cervical cancer?

**We have a detailed understanding of how HPV causes cervical cancer**

Every case of cervical cancer is caused by the same carcinogen: HPV

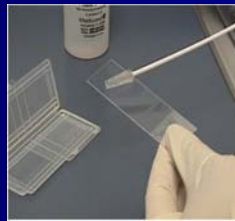
Cervical carcinogenesis develops with a long latency period after the initial infection



## What is unique about cervical cancer?

We have an excellent test for early detection of cervical lesions and cancer

Pap smear programs have resulted in a 70% decrease in cervical cancer incidence



## What is unique about cervical cancer?

We have 2 HPV vaccines that have the potential to prevent over 70% of HPV infections associated with cervical cancer

The vaccines are highly effective in preventing HPV infections with HPVs 16/18



## Questions

- What are the most recent cervical screening guidelines?
- Do the new guidelines really make sense and will we miss cervical cancer in teenagers?
- When should HPV testing be used?

**The scope of the problem....**

## Estimated Annual Incidence of HPV Cervical Infection/Dysplasia<sup>1</sup>

Cervical Infection/Dysplasia	United States	Worldwide
HPV infection without detectable cytologic abnormalities	10 million	300 million
Low-grade dysplasia	1 million	30 million
High-grade dysplasia	300,000	10 million

- **Virtually all cases of cervical cancer come from high-grade dysplasias.**

1. World Health Organization. Geneva, Switzerland: World Health Organization; 1999:1–22.

## Cervical Cancer Stats

- 11,270 women will be diagnosed with and 4,070 women will die of cancer of the cervix uteri in the US in 2009.
- This represents a 70% decrease in the US rate of cervical cancer over the last 80 years, and a 50% decrease over the last 30 years.
- However, it is still the second highest cause of cancer death among women world wide...

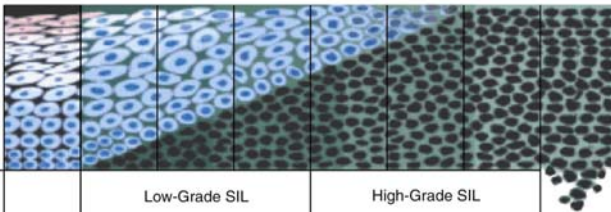
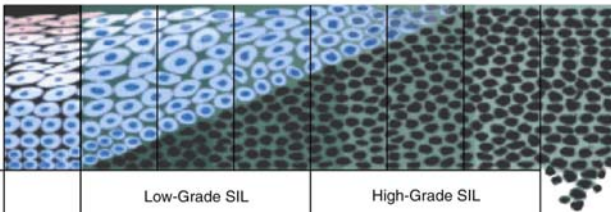
## Who still gets cervical cancer in the US?

- 50% of women who get cervical cancer in US have never been screened
- 10% of women who get cervical cancer in US have not been screened within the past 5 years
- Women who come from other countries where Pap screening is not the norm are at high risk
- Women who use health care episodically are at high risk

## Natural History of CIN/dysplasia

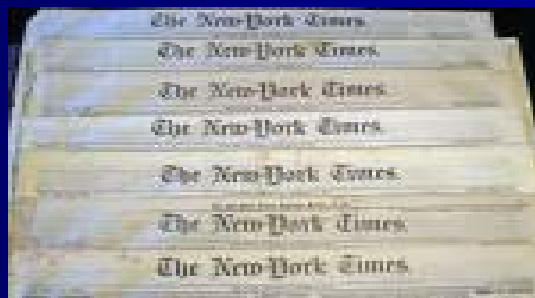
- Linked to presence of high risk/oncogenic HPV
- CIN1: 60% regress
- CIN2: 40% regress
- Higher levels of dysplasia are more likely to progress to cancer
- Smoking increases risk of cervical dysplasia

## Cervical Epithelium Showing Progressive Degrees of Dysplasia and Neoplasia

Surface of epithelium								
Basal membrane								
Cytology	Normal	Low-Grade SIL			High-Grade SIL			Invasive cancer (penetrates basal membrane)
Histology		Condy-lomatous atypia	CIN 1		CIN 2	CIN 3		
Description			Very mild dysplasia	Mild dysplasia	Moderate dysplasia	Severe dysplasia	Carcino-ma <i>in situ</i>	
HPV presence	HPV low-risk types HPV high-risk types				HPV high-risk types			

## Challenges in managing cervical pre-cancers

- Colposcopy is not highly sensitive, and may need to be repeated for an accurate diagnosis
- Lesions may change over time
- Special populations differ with respect to risk of progression/regression (ie. Adolescents, pregnant, immunocompromised)
- Fertility desires may affect relative risk of treatment versus observation



*ACOG issues new guidelines  
November 2009  
(ACOG Practice Bulletin 109)*



- In June 2009, representatives from ACS, ACOG and 25 other organizations met to discuss cervical cancer screening.
- There was general consensus to start screening at age 21.

### ***ACOG guidelines*** ***(ACOG Practice Bulletin 109)***

- Initiate screening at age 21
- Screen every 2 years until 30, then
- If three normal consecutive Paps, and no h/o CIN2/CIN3, DES or HIV, or are not immunocompromised otherwise, may move to Paps q 3 years
- Women who have had a hysterectomy for benign reasons and have no h/o HSIL, may discontinue testing
- Co testing with Pap/HPV is appropriate for low risk women over age 30. If neg/neg rescreen no sooner than 3 years.

**Cervical Cytologic Screening Guidelines from the American College of Obstetricians and Gynecologists, 2009.**

Age	Recommendation for Cytologic Screening
Under 21 yr	Avoid screening
21 to 29 yr	Screen every 2 yr
30 to 65 or 70 yr	May screen every 3 yr*
Between 65 and 70 yr	May discontinue screening†

\* This recommendation applies only to women with three consecutive negative cytologic tests; exceptions include women with human immunodeficiency virus infection, compromised immunity, a history of cervical intraepithelial neoplasia grade 2 or 3, or exposure to diethylstilbestrol in utero.

† This recommendation applies only to women with three or more consecutive negative cytologic tests and no abnormal tests in the preceding 10 years; exceptions include women with multiple sexual partners.

## Additional Recommendations

- Continue to screen and counsel teens re STDs, safe sex and contraception
- Consider discontinuing Pap testing in women ages 65-70 with 3 normal Paps within the prior 10 years
- Women who have been treated for CIN2 or CIN3 need annual screening for at least 20 years
- Women who have had a hysterectomy and have a h/o of CIN2/CIN3 or in whom the pathology cannot be documented should continue screening
- Annual pelvic exams may still be appropriate even if no Pap necessary.

## Cytology techniques

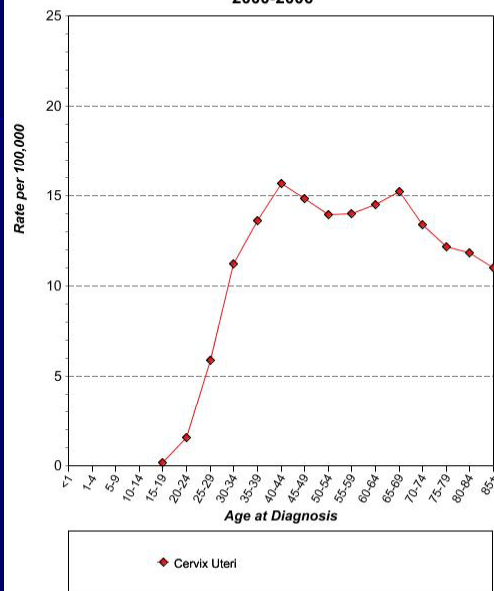
- Both thin layer and conventional Pap acceptable
- Thin layer cytology allow for co-testing for HPV, GC and chlamydia
- No difference in sensitivity for the detection of high grade precursors
- Bethesda 2001 nomenclature should be used to report results and direct practioner to next steps

**Will these guidelines result in increased cervical cancer in teens?**

(i.e. is raising the age to initiate screening dangerous?)

- HPV infections in teens are common but usually resolve spontaneously
- Cervical cancer is extremely rare in teens
- Evaluation of teens results in increase in treatments which may affect long term pregnancy outcomes
- HPV vaccine against 16/18 may result in a decrease in cervical cancer in 15-20 years (when these girls are at greater risk for cancer)

Age-Specific (Crude) SEER Incidence Rates  
By Cancer Site  
All Ages, All Races, Female  
2000-2006



Cancer sites include invasive cases only unless otherwise noted.  
Incidence source: SEER 17 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, Atlanta, San Jose-Monterey, Los Angeles, Alaska Native Registry, Rural Georgia).

## Optimal Screening frequency: *depends on risk*

- For average risk women:
  - Screen at 2 year intervals from 20-30, and if at least three normal consecutive Paps, increase interval to every three years
  - In this group annual screening confers no additional protection and adds cost (NBCCEDP)
  - May add HPV testing after age 30, but if negative/negative do not rescreen before three years

## Women at **increased** risk need annual screening

- HIV infected (screen 2x in first year and then annually if normal)
- Women who are immunosuppressed
- Women with a h/o DES exposure
- Women previously treated for CIN2/ CIN3 or cancer. For this group, annual screening should occur for at least 20 years.

## Will increasing Pap screening interval in **low risk** women increase rates of cervical cancer?

### Risk of Cervical Cancer Associated with Extending the Interval between Cervical-Cancer Screenings

George F. Sawaya, M.D., K. John McConnell, Ph.D., Shalini L. Kulasingam, Ph.D., Herschel W. Lawson, M.D., Karla Kerlikowske, M.D., Joy Melnikow, M.D., M.P.H., Nancy C. Lee, M.D., Ginny Gildengorin, Ph.D., Evan R. Myers, M.D., M.P.H. and A. Eugene Washington, M.D.

N Engl J Med  
Volume 349;16:1501-1509  
October 16, 2003



Average Estimated Number of Additional Tests That Would Be Required to Avert One Case of Invasive Cervical Cancer through Annual Screening Rather Than Screening Performed Once Three Years after the Last Negative Test in Hypothetical Cohorts of 100,000 Women with Three or More Previous Negative Papanicolaou Tests

**Table 5.** Average Estimated Number of Additional Tests That Would Be Required to Avert One Case of Invasive Cervical Cancer through Annual Screening Rather Than Screening Performed Once Three Years after the Last Negative Test in Hypothetical Cohorts of 100,000 Women with Three or More Previous Negative Papanicolaou Tests.

Age	Average No. of Additional Papanicolaou Tests per Case of Invasive Cervical Cancer Averted	Average No. of Additional Colposcopic Examinations per Case of Invasive Cervical Cancer Averted
<30 Yr	42,621	2,364
30–44 Yr	69,665	3,861
45–59 Yr	209,324	11,502
60–64 Yr*	—	—

\* There were no differences in the expected rates of invasive cervical cancer according to screening strategy in this age group.

THE NEW ENGLAND JOURNAL of MEDICINE

## Conclusions

- As compared with annual screening for three years, screening performed once three years after the last negative test in women 30 to 64 years of age who have had three or more consecutive negative Papanicolaou tests is associated with an average excess risk of cervical cancer of approximately 3 in 100,000

THE NEW ENGLAND JOURNAL of MEDICINE

## Age to stop screening

- Highest rates of cervical cancer are in older women.
- Women who have not been screened or who have prior abnormal cytology should continue screening
- Women with multiple new sexual partners may still need screening
- Women aged 65-70 with at least 3 negative Paps within the last 10 years may discontinue screening

## When to discontinue screening after hysterectomy?

- Women who have had a total hysterectomy for benign reasons and have no prior h/o CIN may discontinue screening
- Women with a h/o CIN2/CIN 3 should continue screening
- Women for whom a negative history cannot be documented should continue screening
- The decision to discontinue testing should include both a review of the patient's Pap results prior to hyst and a pathologic confirmation of the hysterectomy specimen



## HPV testing

### HPV Typing: Clinical Utility

- Greater than 100 types
- Only “high-risk” types important
- Common infection—only persistent infections of concern
- More easily cleared in young women

## HPV testing

*HPV more sensitive, but less specific than pap for detecting CIN2+*

- Hybrid Capture 2 and Cervista-FDA approved (2009)
- Hybrid Capture 2 tests for 13 high- and intermediate-risk HPV types—but may cross-react with low-risk types
- Cervista HR tests for 14 high/intermediate types
- Cervista HPV 16/18 tests for HPV 16/18--to be used only in women over 30

## Mechanisms of HPV Transmission and Acquisition

- Sexual contact
  - Through sexual intercourse<sup>1</sup>
  - Genital–genital, manual–genital, oral–genital<sup>2–4</sup>
  - Genital HPV infection in virgins is rare, but may result from nonpenetrative sexual contact.<sup>2</sup>
  - Condom use may help reduce the risk, but it is not fully protective.<sup>2</sup>
- Nonsexual routes
  - Mother to newborn (vertical transmission; rare)<sup>5</sup>
  - Fomites (eg, undergarments, surgical gloves, biopsy forceps)<sup>6,7</sup>
    - Hypothesized but not well documented

## HPV Testing in Adolescents

- Not helpful for reflex testing as up to 80% may test positive
- Most infections in adolescents are transient
- Adolescents may have different subtypes, and testing cannot distinguish between new and persistent infections
- Only persistent infections are worrisome

## HPV Clearance

- In women 15–25 years of age, ~80% of HPV infections are transient.<sup>1</sup>
  - Gradual development of cell-mediated immune response presumed mechanism<sup>2</sup>
- In a study of 608 college women, 70% of new HPV infections cleared within 1 year and 91% within 2 years.<sup>3</sup>
  - Median duration of infection = 8 months<sup>3</sup>
  - Certain HPV types are more likely to persist (eg, HPV 16 and HPV 18).

1. Meijer CJLM, Helmerhorst TJM, Rozendaal L, van der Linden JC, Voorhorst FJ, Walboomers JMM. *Histopathology*. 1998;33:83–86. 2. Schiffman M, Kjaer SK. *J Natl Cancer Inst Monogr*. 2003;31:14–19. 3. Ho GYF, Bierman R, Beardsley L, Chang CJ, Burk RD. *N Engl J Med*. 1998;338:423–428.

## HPV testing in young women (< age 30)

- No role for HPV testing prior to vaccine, as test only detects active infection and may not reflect prior infection (and thus results are not informative).
- No role for primary testing in women under 30 as most infections are cleared and do not confer elevated risk, and there is a high risk of positivity in this age group (with associated anxiety and no improvement in cervical cancer prevention/detection)

*Thus, HPV should never be ordered in an adolescent and only ordered as a reflex test in women between 20 and 30.*

## DNA PAP Test

- FDA-approved (2003) for women over age 30 for primary screening
- No role for women under age 30
- Women who test negative on both are at low risk of developing cervical cancer over 3 - 5 years (Kaiser, 1996)
- Costs of adding HPV cotesting on annual basis are prohibitive (>2 million dollars per year of life saved) and add little benefit (Goldie, et al. Obstet Gynecol 2004)

## Will we be able to primarily screen with HPV?

- **Canadian Screening Trial** (NEJM 2007)

>10,000 women age 30-69

Hc2 and conventional pap

- **Dutch Randomized Screening Trial**  
(Lancet 2007)

17,000 women age 29-56

Conventional pap or pap/pcr HPV

*Results show similar overall detection of dysplasia, but HPV may detect earlier, but with higher percent of women undergoing colposcopy*

### Comparison of Pap Testing and HPV DNA Testing Using Combined Study Groups According to Different Positivity Thresholds and Test Combinations

**Table 4.** Comparison of Pap Testing and HPV DNA Testing Using Combined Study Groups According to Different Positivity Thresholds and Test Combinations.<sup>a</sup>

Screening Approach	Definition of Positivity	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	No. of Tests Needed for Screening	Referrals for Colposcopy
			%				%
Pap only	ASCUS or worse	56.4	97.3	8.5	99.8	9,959	2.9
	LSIL or worse	42.2	99.1	17.5	99.7	9,959	1.0
HPV only	≥1 pg HPV DNA/ml	97.4	94.3	7.0	100.0	9,959	6.1
	≥2 pg HPV DNA/ml	81.1	95.5	9.1	99.9	9,959	4.8
Pap screening followed by HPV triage	Triage of all results of ASCUS; ≥1 pg HPV DNA/ml	53.8	98.7	14.9	99.8	10,145	1.6
HPV screening followed by Pap triage	Triage of all with ≥1 pg HPV DNA/ml; Pap threshold of ASCUS or worse	53.8	99.1	21.4	99.8	10,563	1.1
Pap and HPV cotesting	Pap result of ASCUS or worse, or HPV result of ≥1 pg HPV DNA/ml	100.0	92.5	5.5	100.0	19,918	7.9

<sup>a</sup> Estimates are corrected for verification bias according to the conservative case definition and are based on pooled data from 9959 women in the two study groups who had available Pap and HPV results. HPV denotes human papillomavirus, ASCUS atypical squamous cells of undetermined significance, and LSIL low-grade squamous intraepithelial lesion.

Mayrand MH et al. N Engl J Med 2007;357:1579-1588



**Primary HPV screening of older women may be cost-effective in low resource settings**

## Original Article

**HPV Screening for Cervical Cancer in Rural India**

Rengaswamy Sankaranarayanan, M.D., Bhagwan M. Nene, M.D., F.R.C.P., Surendra S. Shastri, M.D., Kasturi Jayant, M.Sc., Richard Muwonge, Ph.D., Atul M. Budukh, Ph.D., Sanjay Hingmire, B.Sc., Sylva G. Malvi, M.Sc., Ph.D., Ranjit Thorat, B.Sc., Ashok Kothari, M.D., Roshan Chinoy, M.D., Rohini Kelkar, M.D., Shubhada Kane, M.D., Sangeetha Desai, M.D., Vijay R. Keskar, M.S., Raghevendra Rajeshwarkar, M.D., Nandkumar Panse, B.Com., and Ketayun A. Dinshaw, M.D., F.R.C.R.

N Engl J Med  
Volume 360(14):1385-1394  
April 2, 2009

**Conclusion**

- In a low-resource setting, a single round of HPV testing was associated with a significant reduction in the numbers of advanced cervical cancers and deaths from cervical cancer



## Bottom-line HPV info:

- Very common infection
- Most infections resolve—only persistent infections significant
- Infections in teens usually resolve
- Sexually transmitted—skin to skin contact
- Condoms do not fully protect against HPV, although may decrease risk of cervical cancer
- No role for primary screening below age 30

## Looking Towards the Future

- Ultimately a combination of vaccine in younger women and screening for carcinogenic HPV in older women may revolutionize cervical cancer prevention

*See Schiffman, M, Castle, PE. The Promise of Cervical Cancer Prevention. NEJM 353:20, 2101-2104, 2005*