Making Sense of Cervical Cancer Screening

New Guidelines published November 2012

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The incidence of cervical cancer in the US has decreased more than 50% in the past 30 years because of widespread screening with cervical cytology.

1975 - rate was 14.8/100,000 women
2008 - rate was 6.6/100,000 women

Mortality rates:
1975 - 5.55/100,000 women
2008 - 2.38/100,000 women

The American Cancer Society (ACS) estimates there will be 12,170 new cases in US in 2012 with 4,220 deaths.
Cervical cancer is more common worldwide, especially in countries without screening programs.

2008 estimates worldwide: 530,000 new cases and 275,000 resultant deaths yearly.

The decline in the US is due to direct access to screening for cervical cytology.

Women who are immigrants and those who lack a regular source of health care, the uninsured and underinsured are at especially high risk for cervical cancer.
Estimates suggest that 50% women diagnosed with cervical cancer have never had cervical cytology testing

10% of diagnosis have not been screened within the past 5 years.

Thus 60% of diagnoses of cervical cancer is a direct result of inadequate screening.
Natural History of Cervical Neoplasia

HPV is divided into two classes: Oncogenic/Nononcogenic

Oncogenic (High Risk) HPV – is usually a necessary factor but not a predictive component of squamous cervical neoplasia. Only a small fraction of women infected with high risk HPV will develop significant cervical abnormalities and cancer. Most HPV infections are transient and poses little risk of progression. Persistent infection at 1-2 years strongly predicts subsequent risk of CIN 3 or cancer regardless of age.
The HPV genotype appears to be the most important determinant of persistence and progression.

HPV-16- highest carcinogenic potential and accounts for approx. 55-60% of all cases of cervical cancer worldwide

HPV-18- second most carcinogenic potential and accounts for approx. 10-15% of cases.

10 other genotypes are associated with the remainder of cases.

Known co-factors include cigarette smoking, compromised immune system and HIV infection.
HPV infection is most common in teenagers and women in the early 20’s.

These women usually have an effective immune response that clears the infection in average of 8 months, reduces the viral load by 85-90% in 8-24 months.

HPV infection detected in women older than 30 is more likely to be a persistent infection. This correlates with increased rates of HSIL with increasing age.
CIN I is a manifestation of acute HPV infection, high rate of regression is normal and expectant management usually best course of action.

CIN II controversial because of the challenge of accurate diagnosis and uncertainty of ideal management. Prognosis seems to represent a mix of low and high grade lesion difficult to differentiate by histology. The American Society for Colposcopy and Cervical Pathology (ASCCP) and the College of American Pathologists have developed a two tiered histologic classification: LSIL and HSIL which have eliminated the CIN II category.

CIN III poses a significant risk for progression to cancer estimated to 30.1% at 30 years.
When evaluating appropriate screening intervals it is important to consider time required for disease progression.

Most HPV related types of cervical neoplasia are very slow to progress, on average a severe dysplasia may take 3-7 years to progress to invasive cervical cancer.
The 2001 Bethesda System for reporting Cervical Cytology

Specimen type- conventional or liquid based
Specimen adequacy- satisfactory, unsatisfactory
Interpretation:
Negative for intraepithelial lesion or malignancy
Epithelial cell abnormality
Organisms ie… Trichomonas vaginalis, fungal organisms, bacterial vaginosis, actinomyces, HSV, inflammation, radiation reaction, IUD, glandular cells, atrophy
Epithelial cell abnormalities cont.

Atypical Squamous cells
- ASC-US –of undetermined significance
- ASC-H – Cannot exclude HSIL

LSIL- low grade squamous intraepithelial lesion encompasses HPV, mild dysplasia, CIN I

HSIL – high grade squamous intraepithelial lesion encompasses moderate to severe dysplasia, carcinoma in situ, CIN II and CIN III

Squamous cell carcinoma

Atypical Glandular cells AGUS includes endocervical, endometrial and glandular. May specify favor neoplastic

AIS- endocervical adenocarcinoma in situ

Adenocarcinoma or other malignant neoplasms
Human Papillomavirus Testing

FDA has approved several tests for detection of cervical HPV DNA.

Testing is generally for the 13-14 most common high risk genotypes

Testing should be used only to detect the presence of high risk HPV. There is no role for low risk genotype testing.

Should be used to determine need for colposcopy in ASC-US cytology (reflex testing)

As an adjunct to cytology for cervical cancer screening in women 30-65 years (co-testing)
HPV Vaccination

Vaccines are available that can protect against high risk HPV.

One vaccine protects against HPV 16 and 18 (two-type vaccine). Another protects against types 16, 18, 6 and 11. The vaccines trigger the immune system to fight off these viruses if exposure occurs. They do NOT protect against other types of HPV.

Both vaccines are given in three doses over a 6-month period.

Advisory Committee on Immunization Practices of the CDC and ACOG recommends immunization for girls and boys 9-26 years of age

It is predicted that significant reduction in cervical cancer will likely not begin until approx. 20 years after widespread vaccination.
Screening for Cervical CA

Screening should begin at age 21.
Women younger than 21 should NOT be screened regardless of age of sexual initiation or presence of other behavior related risk factors.

Only 0.1% of cases of cervical cancer occur before age 20 which translates to approx. 1-2/1,000,000 females age 15-19.

In a report of 10,090 pap test results in ages 12-18, 422 specimens (5.7%) were reported as LSIL, 55 specimens (0.7%) were HSIL.

Earlier onset of screening may lead to anxiety, morbidity and expense due to overuse of excisional procedures that may produce increased risk of premature deliveries.

Initiation of reproductive health should not be predicated on cervical cancer screening. Education on HPV vaccine, STD’s and safe sexual practices are cornerstone for OB/GYN visits in young women.
Recommended Screening Methods

Women 21-29
Cervical cytology alone every three years. Co-testing should not be performed in women younger than 30 due to high prevalence of high risk HPV infections and low incidence of cervical cancer in sexually active women in this age group.

Stout NK, et al. Published a modeling study in Archives of Internal Medicine 2008 that reported outcomes for women aged 20 years for a 10 year period predicted that the number of colposcopy procedures would be reduced by one half (187/1000 vs 403/1000) if these women were screened every three years and a marginal difference in lifetime cancer risk of 0.69% vs 0.33%
Women aged 30-65
Co-testing with cytology and HPV screening every 5 years is preferred. Screening with cytology alone every 3 years is acceptable.
In women 30 and over a negative cervical cytology with negative high risk HPV DNA test have been shown to be at extremely low risk of developing CIN 2 or CIN 3 during the next 4-6 years.
Several trials have looked at co-testing vs cytology alone found in (Lancet Oncol 2012; 2010; N Engl J Med 2007). Regardless of the frequency of cervical cancer screening, patients should be counseled that annual well-woman visits are recommended even if cervical cancer screening is not performed.
Women with any of the following risk factors may require more frequent screening:

- Infected with HIV
- Immunocompromised (such as those who have received solid organ transplants)
- Exposure to DES in utero
- Women previously treated for CIN 2, CIN 3 or cancer

CDC recommends HIV infected women be screened twice first year after diagnosis and annually, and at age of diagnosis regardless if less than 21.
Women treated for CIN 2 or higher remain at risk of persistent or recurrent disease for at least 20 years. A meta-analysis (Soutter WP et al, *Long term risk of invasive cervical cancer after treatment of squamous cervical intraepithelial neoplasia*. Int J Cancer 2006; 118: 2048-55) demonstrates that these women have a 2.8 fold increased risk of invasive disease. These women should undergo routine age-based screening for 20 years after initial post treatment surveillance even if greater than 65 years of age.
Screening should be discontinued after age 65 in women with adequate negative prior screening and no history of CIN 2 or higher.

Adequate negative screening is defined as three consecutive negative cytology results or two consecutive negative co-test results in previous 10 years, with the most recent result within past 5 years.

In women who have had a hysterectomy with removal of the cervix and never had a CIN 2 or higher, routine cytology screening and HPV testing should be discontinued. Women who have had a history of CIN 2 or higher and have had a hysterectomy with cervix removal should continue to be screened for 20 years after post treatment screening.
Management

ASC-US with negative HPV
- Very low risk of CIN 3 - recommend routine screen
- Studies site 0.28-0.54% risk of CIN 3 in 5 years

Negative cytology with positive HPV
- Repeat co-testing in 12 months if LSIL + or HPV positive refer for colposcopy, if negative routine screening
  Or

Immediate HPV genotype specific testing for 16 alone or 16/18. If positive refer for colposcopy. If negative co-testing in 12 months.
**ASC-H**
- 20-50% risk of CIN2, 3 lesion – colposcopy
- negative colposcopy, repeat cytology and HPV in 12 months.

**LSIL or ASCUS positive HPV**
- 26.7% are found to have CIN2 or higher colposcopy recommended. IF colposcopy negative HPV testing in 12 months or cytology at 6 and 12 months. If testing negative routine screening protocol if positive repeat colposcopy.
HSIL

- Mean reporting rate is 0.7% and varies with age
- Colposcopy identifies CIN2 or higher 53-66% with biopsy confirmation in 84-97%.
- LEEP treatment of choice and can been done at time of colposcopy reducing cost of second procedure.
- Endocervical currettage (ECC) done at time of procedure.
- Cytology every 6 months with 2 negatives may return to routine screening for age.
AGUS or AIS

- Mean reporting rate 0.4%
- Can be associated with Adenocarcinoma of cervix endometrium, ovary or fallopian tube.
- 9-28% diagnosed with AGUS will have significant neoplasia, 3-17% will have invasive cancer.
- Varies with age, older than 35 years higher incident of malignancy.
- Colposcopy with ECC and biopsies optimal for diagnosis. HPV DNA typing at time of colposcopy.
- Cytology with HPV testing if positive must repeat every 6 months until 4 consecutive negatives then return to normal screening. (if less than CIN 2)
Significance of Endometrial Cells in cervical cytology

- Rarely significant in women younger than 40
- Approximately 0.5-1.8% cytology in women over 40 may be associated with significant endometrial pathology.
- Endometrial biopsy is recommended to rule out pathology in this age group.
Treatment modalities

**CIN I (HPV positive), with ASCUS, ASC-H, LSIL**
- observation for 2 years- under 30 cytology every 6 months, over 30 may do HPV typing every 12 months, if positive consider ablation or excision.

**CIN I with HSIL or AGUS**
- diagnostic excisional biopsy with follow up cytology every 6 months for 1 year.

**CIN 2 or CIN 3**
- prevalence of CIN 3 peaks between 25-30 years, untreated progression to cancer generally takes another decade. Excision biopsy by LEEP, CKC with margins negative with close follow up for 20 years.
AIS
-1.25/100,000 women
-Hysterectomy is treatment of choice in woman who have completed childbearing.
-Future fertility desired negative margin excision with close follow up HPV typing, cytology and colposcopy with ECC every 6 months. 20 years of follow up as previously discussed or hysterectomy after completion of childbearing.
All of the recommendations discussed results from a review of the updated guidelines of:
- ACS American Cancer Society
- ASCCP American Society for Colposcopy and Cervical Pathology
- ASCP American Society for Clinical Pathology
- U.S. Preventive Services Task Force recommendations
- Practice Bulletin of ACOG American College of Obstetricians and Gynecologists.
Questions??????