Should these women be screened for cervical cancer? If so, with what test?

- 19 yo single woman with 4 life-time sex partners
- 30 yo married woman with one life-time sex partner
- 50 yo woman who has had a TAH for fibroids
- 66 yo woman who had CIN II at age 30, treated, and all subsequent normal paps
Endometrial Cancer

No screening tests have value

Ovarian Cancer Screening

REF: ACOG Focus on Female Cancers 2009 and USPSTF Recommendation
Background: Ovarian Cancer

- Ovarian cancer is the deadliest gynecologic cancer, taking the lives of over 15,000 women annually in the United States.
- Although the length of survival after diagnosis has increased over past decades with advances in treatment, the overall mortality has shown little improvement.
- In an effort to reduce the impact of this disease, significant focus has been given to both primary prevention and screening, particularly in the high-risk patient population.

Inherited Mutations

- Women with Hereditary Breast and Ovarian Cancer (HBOC) Syndrome (inherited mutations of the BRCA1 and BRCA2 genes) have up to a 45% lifetime risk of ovarian cancer.
- Approximately 10% of epithelial ovarian cancers are due to BRCA1 or BRCA2 mutations.
- Women with Hereditary Non-Polyposis Colorectal Cancer (HNPCC), Lynch II Syndrome, have up to a 12% lifetime risk of ovarian cancer.
**Family History**

- Women who have one first degree relative with ovarian cancer have a 3-5% lifetime risk of developing the disease.

**Factors Increasing Risk Of Ovarian Cancer**

- Infertility
- Endometriosis
- Low parity
- Early menarchal age
- Late menopausal age
- Living in a Western industrialized country
Protective Factors

• Oral contraceptive use

• Pregnancy

• Tubal ligation

• Hysterectomy

• Breast feeding

• Prophylactic bilateral salpingo-oophorectomy (BSO) in high-risk women can reduce the risk of ovarian cancer by approximately 90%

Challenges Of Screening For Ovarian Cancer

• Low prevalence of disease

• No tests currently available with adequate sensitivity, specificity or PPV to effectively screen for ovarian cancer

• High number of false positive tests, which would result in an unacceptable number of women who would be subjected to invasive procedures

• Screening has not been shown to reduce mortality from ovarian cancer, even in high-risk patients
Tests Available For Ovarian Cancer Screening

• CA 125 and transvaginal ultrasound (TVS)

• CA 125 is not sensitive for early disease and is elevated in a number of benign conditions, even in older women

• TVS is not reliable in distinguishing benign from malignant tumors and its use in the asymptomatic patient can lead to unnecessary surgery

• Either test alone is not as effective as using both, although this also does not achieve adequate sensitivity, specificity or positive predictive value

Bottom Lines for Ovarian Cancer Screening

• Routine screening for ovarian cancer should not be performed. Emphasize to patients the high number of false positive tests and the associated risks of unnecessary surgery.

• Routinely perform a risk assessment with all patients, specifically asking about a family history of ovarian cancer as well as other cancers including breast, colorectal and endometrial cancers.

• Refer to a genetic counselor when appropriate.

• When counseling patients on birth control options, highlight the significant decrease (up to 60%) in risk of ovarian cancer associated with oral contraceptive pill use.

• Encourage patients to adopt a healthy lifestyle.

• Review the Hereditary Breast and Ovarian Cancer (HBOC) chapter of this resource guide, and the April 2009 ACOG Practice Bulletin on HBOC syndrome for more information on screening and prevention in the high-risk patient.
USPSTF Statement

- The U.S. Preventive Services Task Force (USPSTF) recommends against routine screening for ovarian cancer. Rating: D Recommendation.

- Rationale: The USPSTF found fair evidence that screening with serum CA-125 level or transvaginal ultrasound can detect ovarian cancer at an earlier stage than it can be detected in the absence of screening; however, the USPSTF found fair evidence that earlier detection would likely have a small effect, at best, on mortality from ovarian cancer. Because of the low prevalence of ovarian cancer and the invasive nature of diagnostic testing after a positive screening test, there is fair evidence that screening could likely lead to important harms. The USPSTF concluded that the potential harms outweigh the potential benefits.

Cervical Cancer Screening
**Guidelines as of October 2011**

- Following are the cervical cancer screening guidelines from the ACS, ACOG, and USPSTF
- They are getting closer together
- ACS reaffirmed their guidelines in 2009 and the ACOG guidelines are brand new as of December 2009
- The USPSTF has not revised their guidelines on cervical cancer screening since 2003, but will in 2012
- New guidelines are under review and coming in 2012

**American Cancer Society Guidelines 2009**

- All women should begin cervical cancer screening about 3 years after they begin having vaginal intercourse, but no later than 21 years old. Screening should be done every year with the regular Pap test or every 2 years using the newer liquid-based Pap test.
- Beginning at age 30, women who have had 3 normal Pap test results in a row may get screened every 2 to 3 years. Women older than 30 may also get screened every 3 years with either the conventional or liquid-based Pap test, plus the human papilloma virus (HPV) test.
- Women 70 years of age or older who have had 3 or more normal Pap tests in a row and no abnormal Pap test results in the last 10 years may choose to stop having Pap tests.
- Women who have had a total hysterectomy (removal of the uterus and cervix) may also choose to stop having Pap tests, unless the surgery was done as a treatment for cervical cancer or pre-cancer. Women who have had a hysterectomy without removal of the cervix should continue to have Pap tests.
ACOG Guidelines 2009

- Women from ages 21 to 30 be screened every two years instead of annually, using either the standard Pap or liquid-based cytology.
- Women age 30 and older who have had three consecutive negative cervical cytology test results may be screened once every three years with either the Pap or liquid-based cytology.
- Women with certain risk factors may need more frequent screening, including those who have HIV, are immunosuppressed, were exposed to diethylstilbestrol (DES) in utero, and have been treated for cervical intraepithelial neoplasia (CIN) 2, CIN 3, or cervical cancer.
- Routine cervical cytology testing should be discontinued in women (regardless of age) who have had a total hysterectomy (removal of the cervix along with the uterus) for noncancerous reasons, as long as they have no history of high-grade CIN.
- It is reasonable to stop cervical cancer screening at age 65 or 70 among women who have three or more negative cytology results in a row and no abnormal test results in the past 10 years.

ACOG Explanations

"Moving the baseline cervical screening to age 21 is a conservative approach to avoid unnecessary treatment of adolescents which can have economic, emotional, and future childbearing implications. ACOG previously recommended that cervical screening begin three years after first sexual intercourse or by age 21, whichever occurred first. Although the rate of HPV infection is high among sexually active adolescents, invasive cervical cancer is very rare in women under age 21. The immune system clears the HPV infection within one to two years among most adolescent women. Because the adolescent cervix is immature, there is a higher incidence of HPV-related precancerous lesions (called dysplasia). However, the large majority of cervical dysplasias in adolescents resolve on their own without treatment."
USPSTF 2003

- The USPSTF strongly recommends screening for cervical cancer in women who have been sexually active and have a cervix.
  - Rating: A recommendation.
- The USPSTF recommends against routinely screening women older than age 65 for cervical cancer if they have had adequate recent screening with normal Pap smears and are not otherwise at high risk for cervical cancer.
  - Rating: D recommendation.
- The USPSTF recommends against routine Pap smear screening in women who have had a total hysterectomy for benign disease.
  - Rating: D recommendation.
- The USPSTF concludes that the evidence is insufficient to recommend for or against the routine use of new technologies to screen for cervical cancer.
  - Rating: I recommendation.
- The USPSTF concludes that the evidence is insufficient to recommend for or against the routine use of human papillomavirus (HPV) testing as a primary screening test for cervical cancer.
  - Rating: I recommendation.
- Rationale: The USPSTF found poor evidence to determine the benefits and potential harms of HPV screening as an adjunct or alternative to regular Pap smear screening. Trials are underway that should soon clarify the role of HPV testing in cervical cancer screening.

Cervical Cancer Screening: The Evidence
Liquid-based Pap Smears Are No Better Than Conventional Cervical Cytology: Meta-analysis

- This meta-analysis included randomized controlled trials and cohort studies in which all patients were submitted to gold standard verification with colposcopy and the histology of colposcopically directed biopsies.
- There were 8 cohort studies and 1 large randomized controlled trial that met inclusion criteria.
- The pooled sensitivity of liquid-based and conventional cytology was not significantly different. There was no difference between methods when high-grade or low-grade squamous intraepithelial lesion was used for calculating relative specificity.
- When ASCUS was used as a cut-off for an abnormal test result, liquid-based cytology had a lower specificity (0.91; 95% CI, 0.84-0.98).


Liquid-based Pap Smears Are Not More Accurate Than Conventional Pap Smears: Large RCT

- RCT of ThinPrep vs conventional cytology
- 89,784 women, aged 30 to 60 years, who participated in a Dutch cervical screening program consisting of Pap testing every 5 years
- Women with an initial abnormal screening test result were followed up for 18 months with either repeat Pap testing or colposcopy with or without biopsy using standard international guidelines.
- Complete follow-up occurred for more than 99% of participants at 18 months.
- 2474 women with cytological abnormalities were identified. Detection rates and positive predictive values for CIN 1, 2, 3, and cervical cancer were similar in both screening groups, indicating that liquid-based cytology is neither more sensitive nor more specific than conventional Pap testing.

HPV Screening Is More Sensitive Than Pap Smears, But The Difference Is Very Small

• Meta-analysis of patient level data from 7 separate studies conducted in 6 European countries to determine the effectiveness of using HPV as a screening tool for high-grade CIN (3 or above).

• 24,295 women were enrolled. All women received initial screening for HPV and cervical cytology at and at various intervals for 6 years. 1.6% of women developed CIN3 or higher.

• 0.27% of women (95% CI, 0.12% - 0.25%) with a negative HPV developed high-grade neoplasia; negative predictive value of 99.7%.

• 0.97% of women (95% CI, 0.53% - 1.34%) with initial normal pap smear developed CIN3 or higher during the 6 years of follow-up; NPV of 99.0%.

Adding HPV Testing To Cytology

• RCT of cervical cancer screening in 17,155 women in Netherlands

• The addition of HPV DNA testing to cytology was compared with conventional cytology alone. Women 29 to 56 with no history of CIN2 or greater were invited to participate.

• Standard screening occurs at 5-year intervals with follow up of abnormal results over an 18-month period. 6.5 years, or 2 screening rounds and follow-up

• After 5 years, HPV DNA testing was performed in both groups.

• There were more CIN3+ lesions detected in the HPV testing group at baseline (68 vs 40; NNS = 306; 95% CI, 175-1111). The second round detected more CIN3+ in the usual care group; no difference in CIN3+ lesions between groups after round 2.

• 2 cancers detected in the HPV screening group and 5 in the usual care group
**HPV Testing: The CCCaST Trial**

- First report of the Canadian Cervical Cancer Screening Trial (CCCaST), to compare HPV testing with cytology as stand-alone tests for CIN 2/3
- 10,154 women, aged 30 years to 69 years. All received both tests. Colposcopy directed biopsy was the reference standard.
- Women with abnormal results from either test AND a random sample of women with normal results, were referred for colposcopy. Atypical cells of uncertain significance (ASCUS) were considered abnormal and an indication for referral to colposcopy.
- Sensitivity of HPV testing for CIN 2 and 3 was 95% (95% CI, 84%-100%) and for cytology was 55% (34%-77%). Specificities were 94% (93%-95%) and 97% (96%-97%), respectively. Bottom-line: Human papillomavirus (HPV) testing is more sensitive, and only slightly less specific, than cervical cytology for the detection of high-grade cervical intraepithelial neoplasia (CIN).


**New Proposed Guidelines for Cervical Cancer Screening October 19, 2011 Are Under Review**

- Historic meeting in 2011 of
  - US Preventive Services Taskforce
  - American Cancer Society
  - American Society for Colposcopy and Cervical Pathology
  - American Society for Clinical Pathology

- Trying to make guidelines consistent!
Cervical Cancer Screening Guidelines
Harmonization Efforts

- The American Cancer Society (ACS), American Society for Colposcopy and Cervical Pathology (ASCCP), and American Society for Clinical Pathology (ASCP) and the US Preventive Services Task Force (USPSTF), in a productive collaboration, have coordinated the release of their respective draft recommendation statements for cervical cancer screening on October 19, 2011.

- The ACS-ASCCP-ASCP draft recommendations are available for your review and feedback at www.asccp.org/practice-management/molecular-screening-symposium


- The GRADE system was used in formulating the ACS-ASCCP-ASCP guidelines: http://www.gradeworkinggroup.org/

Proposed ACS/ASCCP/ASCP Guidelines

- Changes include:

  • Instead of beginning screening 3 years after starting sexual intercourse, the new starting age will be 21 years. This applies equally to women who have and have not been vaccinated against HPV.

  • Pap testing (conventional or liquid based) is recommended every 3 years for women 21 to 29 years of age. This replaces the current recommendation for annual testing with a conventional Pap test or testing every 2 years with a liquid-based Pap test.

  • Pap testing is recommended every 3 years for women 30 years and older, although the preferred strategy is Pap testing plus HPV testing every 3 to 5 years.

  • It is recommended that women who have had normal results on 3 Pap tests in a row, or if over the past 10 years there have not been any abnormal Pap tests and 2 or more HPV tests have been negative, testing can be stopped at 65 instead of 70 years of age.

  • In addition, the draft ACS/ASCCP/ASCP document states that there is insufficient evidence to recommend for or against a comprehensive program for primary screening with HPV testing alone.
New Proposed USPSTF Guidelines

• Similarly, the draft document from the USPSTF recommends:
  • No screening in women younger than 21 years of age, regardless of sexual history
  • Screening with Pap tests every 3 years in women 21 to 65 years of age
  • No screening in women older than 65 years of age who have had adequate previous screening and who are not otherwise at high risk for cervical cancer.

• However, the USPSTF differs in its guidelines on the use of HPV testing, recommending against its use in women younger than 30 years of age, either alone or in combination with Pap tests. The USPFT concludes that there is "insufficient" evidence to assess the balance of benefits and harms of HPV testing, alone or in combination with cytology, for screening for cervical cancer in women 30 years and older.

Back to our cases...

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• 30 yo married woman with one life-time sex partner
• 50 yo woman who has had a TAH for fibroids
• 66 yo woman who had CIN II at age 30, treated, and all subsequent normal paps
• Others?
Cleveland Clinic

Every life deserves world class care.