



Should primary cervical cancer screening of women 30 years and older include HPV testing?

Yes These two important studies provide further evidence that testing for human papillomavirus (HPV) merits a prominent place in primary cervical cancer screening in developed and developing nations.

Sankaranarayanan and colleagues found that a single round of HPV testing in a low-resource setting (rural India) significantly reduced the incidence of advanced cervical cancer and associated mortality. Castle and associates demonstrated that the number of HPV-positive findings among women 30 years and older was not excessive when the HPV and Pap tests were used together (cotesting). In addition, with cotesting, the screening interval for women who tested negative on both tests could be extended to 3 years.

Sankaranarayanan R, Nene BM, Shastri SS, et al. HPV screening for cervical cancer in rural India. N Engl J Med. 2009;360:1385-1394.

Castle PE, Fetterman B, Poitras N, Lorey T, Shaber R, Kinney W. Five-year experience of human papillomavirus DNA and Papanicolaou test cotesting. Obstet Gynecol. 2009;113:595-600.

▶ EXPERT COMMENTARY

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Sankaranarayanan and colleagues report the long-term follow-up of 130,000 women in rural India, who were randomized in 1999 to receive a single screen using one of the following:

- conventional Pap test
- HPV test (Hybrid Capture 2)

- visual inspection of the cervix with acetic acid (VIA)
- no screen (the current standard in India).

Within 8 years of a single HPV test, the incidence of both advanced cervical cancer and cervical cancer mortality declined significantly. In contrast, neither a single Pap test nor a single VIA had a substantial impact on either the incidence of advanced cervical cancer or mortality. Not a single cancer occurred among the 90% of women who tested negative for HPV at enrollment.

Properly timed, the HPV test can avert more advanced cervical cancers and deaths in developing countries than other screening methods

The burden of cervical cancer is shouldered largely by the developing world, where an estimated 80% of the nearly 500,000 cervical cancers occur annually, and where screening has been too costly and complicated to instigate. This study provides the first evidence that a single screen with an HPV test, best performed 15 to 20 years after the median age of first intercourse, would save more lives than other options and may be affordable.

A low-cost, simple, and highly sensitive HPV test (careHPV test) has been developed, with financial backing from the Bill and Melinda Gates Foundation, through the Alli-

WHAT THIS EVIDENCE MEANS FOR PRACTICE

More and more, data point to cotesting as the screen of choice for women 30 years and older, with the screening interval extended to 3 years for any patient who tests negative on both HPV and Pap tests.

» J. THOMAS COX, MD

FAST TRACK

The number of HPV-positive findings among women 30 years and older was not excessive with cotesting (i.e., HPV and Pap tests used together)



ance for Cervical Cancer Prevention. This test provides results within 3 hours and is now being used in demonstration projects in several countries. This appears to offer a way to prevent thousands of deaths from cervical cancer worldwide.

In the United States, cotesting is more effective—and affordable—than the Pap test alone

Castle and associates provide in-depth information on cotesting in women 30 years and older using both the Pap and HPV tests in primary screening in a US setting.

A major concern about cotesting has been that the addition of the HPV test might burden the system with too many positive results, but this study demonstrates otherwise. In the general population of women of this age, the number of HPV-positive results is not burdensome.

In 2003, Kaiser Permanente Northern California instigated cotesting of all women 30 years and older who elected this screening option. Over the next 4 years, nearly 813,000 cotests were performed on more than 580,000 women (median age, 44 years). Overall, 6.27% tested positive for high-risk HPV using Hybrid Capture 2. Among the 93% of women who tested negative for high-risk HPV, the risk of missed precancer and cancer was extremely low, because HPV testing detects most of the 25% to 50% of these lesions missed by a single Pap test.

The authors point out that, for the 90% of women who tested negative on both the Pap and HPV tests, the risk of incipient precancer or cancer is likely to be very low for the next 10 years or so. Therefore, most women who undergo cotesting could be safely screened

at 3-year intervals, and those screened more irregularly would likely be better protected than women screened by cytology alone. Extending the interval makes cotesting more cost-effective and has other benefits, as well.

Rate of HPV-positive findings varied by age

Among women 30 years of age and older, there is some variation in the rate of HPV-positive results. In this study, HPV-positive results were found in:

- 10.8% of women 30 to 34 years old
- 8.0% of women 35 to 39
- 6.3% of women 40 to 44
- 4.9% of women 45 to 49
- 4.3% of women 50 to 54
- 3.9% of women 55 to 59
- 3.7% of women 60 to 69
- 5.3% of women 80 years and older.

The highest rate of HPV was found among women in their 30s. This is the same age group that has the highest rate of high-grade precancer (cervical intraepithelial neoplasia grade 2,3) in the Kaiser health system.

Findings are in line with other studies

The study by Castle and colleagues is the largest general-population screening investigation of cotesting published so far. The rate of HPV-positive and Pap-negative findings was 3.99% for the group of women 30 years and older, which is right on target with the 3.7% rate for cotesting demonstrated in the Netherlands and the 4% rate reported in a US survey by the College of American Pathologists. All women of this age in the Kaiser system were given the option of continuing to get an annual Pap or switching to cotesting every 3 years; 91.6% chose the cotesting option.



Most women who undergo cotesting could choose to extend the cervical-screening interval to 3 years

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BY CHARLES J. DUNTON, MD (EXAMINING THE EVIDENCE, MARCH 2008)

Is ovarian Ca screening effective in postmenopausal women?

Maybe The findings from a study in the United Kingdom indicate that ovarian cancer screening is **effective** in women 50 to 74 years of age. Findings from a US National Cancer Institute-funded study, on the other hand, suggest that it is **ineffective** in a similar group of postmenopausal women.

Menon U, Gentry-Maharaj A, Hallett R, et al. Sensitivity and specificity of multimodal and ultrasound screening for ovarian cancer, and stage distribution of detected cancers: results of the prevalence screen of the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS). *Lancet Oncol.* 2009;10:327-340.

Partridge E, Kreimer AR, Greenlee RT, et al, for the PLCO Project Team. Results from four rounds of ovarian cancer screening in a randomized trial. *Obstet Gynecol.* 2009;113:775-782.

► EXPERT COMMENTARY

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Ovarian cancer is relatively rare, but late diagnosis leads to a higher death rate than the death rate observed with other gynecologic malignancies. Detection at an early stage (I or II) is associated with higher survival than detection at a later stage (III or IV).

Earlier studies have suggested that ovarian cancer screening with the serum biomarker CA 125 and transvaginal ultrasonography (TVS) may help the clinician diagnose ovarian cancer at an earlier stage.

British study finds screening to be effective

In the United Kingdom Collaborative Trial of Ovarian Cancer Screening, postmenopausal women 50 to 74 years old were randomized to one of the following:

- no screening (n = 101,359)
- annual assessment of CA 125 using a

proprietary risk-of-cancer algorithm, with TVS as a second-line test (multimodal screening, or MMS) (n = 50,078)

- annual TVS in a 2:1:1 ratio (n = 48,230). (A scan was considered abnormal when one or both ovaries had complex morphology or a simple cyst exceeded 60 cm³ in size.)

The mean age at screening was 60.6 years, and 96.5% of participants were white.

Women who underwent MMS were triaged according to their estimated risk of developing ovarian cancer, based on the CA 125 level and age-specific risk estimates. Women in the group with the lowest risk of ovarian cancer continued annual assessment of CA 125, whereas those at highest risk underwent repeat measurement of CA 125, followed by TVS if the repeat assay suggested elevated risk. If TVS findings were also abnormal, the patient underwent clinical evaluation.

In the MMS and TVS groups, 8.7% and 12.0% of subjects, respectively, underwent clinical assessment, and surgery was performed in 0.2% and 1.8%, respectively. A primary ovarian or tubal cancer was diagnosed in 42 and 45 women in the MMS and TVS groups, respectively. In addition, 8 (MMS) and 20 (TVS) borderline malignancies were identified.

Overall, 48.3% of invasive cancers were diagnosed during stage I or II, with no difference in the distribution of stages between MMS and TVS groups. The positive predictive value (PPV) of MMS and TVS for primary in-

**FAST
TRACK**

Two large trials found different levels of efficacy for ovarian cancer screening in the general postmenopausal population

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Until we have further data on the value of ovarian cancer screening in postmenopausal women, we should continue the current practice of screening only symptomatic or very-high-risk women for ovarian cancer.

» ANDREW M. KAUNITZ, MD



vasive epithelial and tubal cancers was 35.1% and 2.8%, respectively. The ratio of surgery to case of invasive ovarian cancer was 2.9:1 (MMS) and 35:1 (TVS).

In the US study, women underwent both CA 125 assessment and TVS

The US study involved four annual rounds of screening in women 55 to 74 years old, who underwent both CA 125 measurement and TVS imaging in each round. A CA 125 level of 35 U/mL or above, or ovarian volume greater than 10 cm³ (or detection of an ovarian cyst with complex morphology) was considered abnormal.

Of 34,621 women randomized to screening, 30,630 underwent at least one screen during the four rounds. Almost two thirds of participants were 55 to 64 years old, and almost 89% were non-Hispanic white.

The percentage of women who had at least one positive screen decreased over the four rounds of screening, from 5.8% in year 1 to 4.9%, 4.6%, and 4.5% in years 2 through 4, respectively. In each round of screening, TVS was more likely to be positive than was CA 125 measurement (e.g., 4.6% vs 1.4% in the first round).

Of the 28,746 women who underwent the initial (prevalence) screen, 1,675 (5.8%) had positive findings, 566 (1.97% of those who were screened) underwent surgery, and 27 neoplasms were detected (0.06% of those who were screened), including 18 ovarian or primary peritoneal invasive cancers. Nine borderline tumors were also identified.

The PPV of a positive screen in the first round was 1.1%. Of the 18 invasive cancers identified in this round, 16.7% were diag-

nosed during stage I or II, and 83.4% were identified during stage III or IV. The ratio of surgery to cases of invasive ovarian cancer was 31.4:1.

Why did the trials have different findings?

The findings of the UK study suggest that an MMS strategy of CA 125 assessment, followed selectively by TVS, can detect early-stage ovarian cancer with an acceptable PPV and ratio of surgery to case of invasive cancer.

In contrast, the US findings are discouraging because of the low PPV, the large percentage of malignancies detected at an advanced stage, and the high ratio of surgery to cases of invasive cancer.

Although the studies had different primary outcomes—ovarian and tubal cancers in the UK and ovarian and primary peritoneal cancers in the US—a majority of invasive malignancies detected in both studies were ovarian.

In the US study, the poor performance of screening may be due, in part, to universal rather than selective use of TVS; that modality generates substantially more false positives than does CA 125. The US study also defined an ovarian abnormality more broadly (volume greater than 10 cm³) than the British study did (volume greater than 60 cm³), which may have lowered the PPV in the US trial.

As investigators in the UK continue to follow participants and report their findings, we will learn more about the value of MMS, including its impact on cancer mortality, possibly as soon as 2014. 📌

FAST TRACK

Findings of the UK study suggest that CA 125 assessment, followed selectively by TVS, can detect early-stage cancer with acceptable PPV

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