

Karen H. Lu, MD

OBG MANAGEMENT Board of Editors; Associate Professor, Department of Gynecologic Oncology, University of Texas M.D. Anderson Cancer Center, Houston

Michael R. Milam, MD, MPH

Fellow, Department of Gynecologic Oncology, University of Texas M.D. Anderson Cancer Center, Houston

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GYNECOLOGIC ONCOLOGY

Four recent studies add to what we understand about screening and prophylaxis for ovarian and breast Ca

Obgyns perform most of the screening for cancers of the ovary and breast. The first cancer is especially lethal, though rare, and the second is especially feared among women. This update reviews screening guidelines and recent studies that may affect how we detect and prevent ovarian and breast cancers.

Among the findings:

- In the only multicenter, prospective, randomized, controlled study to date to look at the use of CA-125 and transvaginal ultrasound screening in a low-risk population of postmenopausal women in the United States, researchers found **no evidence to suggest a need to revise the present (1996) ovarian cancer screening guidelines** of the US Preventive Services Task Force.
- Using a Markov decision-analysis

model, investigators explored the health effects of prophylactic bilateral salpingo-oophorectomy in women at average risk of ovarian cancer undergoing hysterectomy. They found that **removing the ovaries may decrease overall survival.**

- Investigators found the opposite to be true in women with BRCA1 or BRCA2 mutations. **Prophylactic bilateral salpingo-oophorectomy greatly reduced the overall mortality rate**, as well as the risk of ovarian and breast cancer.
- In a prospective cohort study of BRCA mutation carriers with no history of breast cancer who underwent prophylactic oophorectomy, **researchers found the short-term use of hormone replacement therapy to be safe**, with no loss of protection against breast cancer.

No need to revise screening guidelines for ovarian cancer

Buys S, Partridge E, Greene M, et al; for the PLCO Project Team. Ovarian cancer screening in the Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trial: findings from the initial screen of a randomized trial. *Am J Obstet Gynecol.* 2005;193:1630-1639.

The need to identify a marker for the early detection of ovarian cancer is especial-

ly urgent, given that approximately 75% of women with the cancer present with late-stage disease. Because the disease is rare, finding a cost-effective screening test with good sensitivity and very high specificity (to decrease too many false-positive results) will be challenging.

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So far, no prospective, randomized studies of any ovarian cancer screening modality have demonstrated a decrease in mortality—the gold standard of efficacy for any screening test. Therefore, the Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer trial is a critical study—it is the only multicenter, prospective, randomized, controlled study in the United States to tackle the question of whether CA-125 and transvaginal ultrasonographic (US) screening will be effective in a low-risk population of postmenopausal women aged 55 to 74.

In this large study, 1 arm underwent ovarian cancer screening with both modalities and the other arm underwent no such screening.

This study reports on baseline, or 'prevalent,' cancers

This preliminary report does not comment on the efficacy of ovarian cancer screening; data on the effect of repeated annual screens on detection rates and mortality will become available over the next several years.

Rather, the purpose of this preliminary report was to detail the baseline ovarian cancer screening tests of the 39,115 women randomized to the intervention arm from November 15, 1993, to December 13, 2001. These results describe “prevalent” cancers—that is, cancers that are present on the first screen. The more important information about efficacy of screening will come over the next several years, as “incident” cancers develop.

Roughly 6% of women had at least 1 abnormal finding at baseline

Among 28,506 women with results for both baseline tests, 1,706 had at least 1 abnormal finding:

- 1,338 had an abnormal transvaginal US scan
- 402 had an abnormal level on the CA-125 test
- 34 had abnormalities in both tests

- 29 malignant neoplasms were identified in this population, 20 of them invasive.

When combined, CA-125 and transvaginal ultrasonography had good positive predictive value

In general, a positive predictive value (PPV) of more than 10% (ie, 10 surgeries to detect 1 cancer) is considered reasonable justification for a screening test. In the PLCO trial, the PPV was 4% for CA-125 alone (16 neoplasms in 402 positive screens), 1.6% for transvaginal ultrasonography alone (22 neoplasms in 1,338 positive screens), and 26.5% if both tests were abnormal (9 neoplasms in 34 positive screens).

When tumors of low malignant potential were excluded, the PPV was 3.7% for an abnormal CA-125, 1.0% for an abnormal transvaginal sonogram, and 23.5% if both tests were abnormal. A PPV of 23.5% for both tests is fairly good (ie, approximately 4 surgeries to detect 1 cancer). However, if only women in whom both screening tests were abnormal went to surgery, 12 of 20 invasive cancers would be missed.

Bottom line: Routine screening still not justified

Nothing in the findings reported here suggests that we need to revise the current (from 1996) ovarian cancer screening guidelines of the US Preventive Services Task Force,¹ which state that “routine screening for ovarian cancer by US, the measurement of serum tumor markers, or pelvic examination is not recommended.”

We will need to wait until the PLCO trial results come in to see the effect of repeated annual ovarian cancer screens on detection rates and mortality. ■

Reference

1. US Preventive Services Task Force. Guide to Clinical Preventive Services. 2nd ed. Baltimore: Williams & Wilkins; 1996. Available at: <http://odphp.osophs.dhhs.gov/pubs/guidecps/>. Accessed June 4, 2007.

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FAST TRACK

Do not screen routinely for ovarian Ca—as current guidelines state, nothing in the literature necessitates this practice

Consider ovarian conservation in hysterectomy for benign disease

Parker W, Broder MS, Liu Z, Shoupe D, Farquhar C, Berek JS. Ovarian conservation at the time of hysterectomy for benign disease. *Obstet Gynecol.* 2005;106:219-226.

As discussed earlier, we have no good screening tool for the early detection of ovarian cancer. Although rare, ovarian cancer is a lethal, scary disease, and most ObGyns prophylactically remove the ovaries at the time of hysterectomy in most postmenopausal and many perimenopausal women.

The downside to this strategy seems low among postmenopausal women, and the upside, in terms of not having to worry about ovarian cancer, seems high. The study by Parker and colleagues, while having definite limitations, asks us to question this routine practice pattern. The authors found that prophylactic oophorectomy may be associated with decreased overall survival.

Model used SEER data, Nurses' Health Study to predict survival

Parker and colleagues used a Markov decision-analysis model (a hypothetical mathematical model that uses published data to create cohorts of patients to estimate risk of morbidity or mortality, or both, over time) to evaluate the risks and benefits of ovarian conservation at the time of hysterectomy for benign disease. Age-specific mortality estimates for ovarian cancer were based on Surveillance, Epidemiology and End Results (SEER) statistics.

For women at average risk of ovarian cancer, the probability of surviving to 80 years of age after hysterectomy between 50 and 54 years varied, and was 62.8% and 62.5% for ovarian conservation with and without estrogen therapy, respectively, compared with 62.2% and 53.9% for oophorectomy with and without estrogen therapy. The main reason that the model found de-

creased overall survival with prophylactic oophorectomy was an increase in coronary artery disease after oophorectomy—a finding that was based on data from the Nurses' Health Study.

At the very least, think hard about the decision to remove the ovaries

This report estimated that about 300,000 prophylactic oophorectomies are carried out annually in the United States. Although this study has limitations, we believe it encourages debate and reexamination of the benefit of prophylactic oophorectomy for benign indications in young, low-risk patients.

The most important finding from the study is that oophorectomy conferred no survival advantage. Given the rarity of ovarian cancer among the general population, this effect is not that surprising.

For now, careful risk assessment remains a fundamental component of management, so that women who are at increased risk of ovarian cancer can undergo prophylactic salpingo-oophorectomy.

For low-risk women, who constitute the majority of patients, the data to support removing ovaries at the time of hysterectomy are less clear.

Make sure the patient understands the low risk of cancer and possible cardiac benefits of preservation

- Conduct a thorough discussion with the patient about the pros and cons of oophorectomy for benign disease.
- The risk of ovarian cancer in the general population is low; patients should understand that they may derive cardiac protection from postmenopausal ovarian function.

FAST TRACK

Oophorectomy confers no survival advantage when performed prophylactically for benign disease

CONTINUED

Do consider oophorectomy among carriers of a BRCA mutation

Domchek SM, Friebel TM, Neuhausen SL, et al. Mortality after bilateral salpingo-oophorectomy in BRCA1 and BRCA2 mutation carriers: a prospective cohort study. *Lancet Oncol*. 2006;7:223-229.

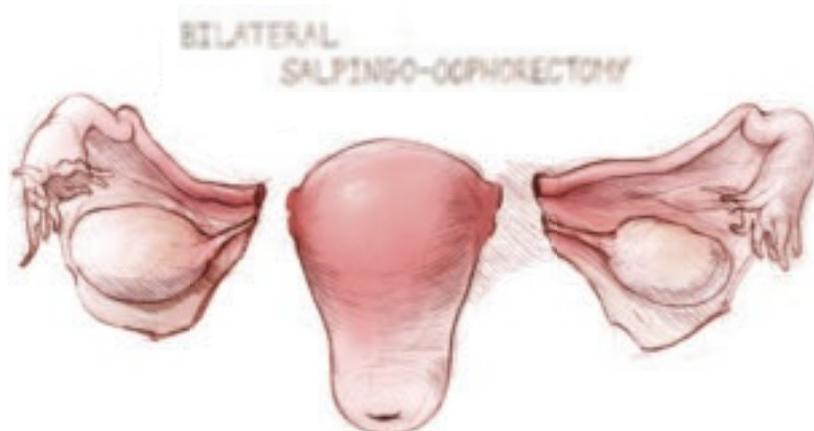
Women known to have BRCA1 or BRCA2 mutations are now managed by means of surveillance or with prophylactic bilateral salpingo-oophorectomy. Although bilateral salpingo-oophorectomy has been shown to reduce the risk of ovarian cancer by 90% and the risk of breast cancer by 50%, until this study few data shed light on the effect of the procedure on overall mortality among women with BRCA mutations.

This prospective cohort study identified 155 patients with BRCA1 or BRCA2 mutations who elected to undergo bilateral salpingo-oophorectomy and matched them by age with a control group of 271. All women were followed until death by any cause or by breast, ovarian, or primary peritoneal cancer. The women were followed for a mean of 3.1 years in the bilateral salpingo-oophorectomy group and 2.1 years in the control group.

Overall and cancer-specific survival improved with oophorectomy

Among BRCA mutation carriers, women who chose prophylactic bilateral salpingo-oophorectomy had improved overall and cancer-specific survival, compared with women who did not undergo the surgery.

In the analysis of the matched BRCA mutation carriers, women who chose to undergo the procedure had a decreased risk of overall mortality (hazard ratio [HR] = 0.24; 95% confidence interval [CI], 0.08-0.71); they also had a decreased risk of mortality due to both breast cancer (HR = 0.1; 95% CI,



0.02-0.71) and ovarian cancer (HR = 0.05; 95% CI, 0.01-0.46).

Practice recommendations

Apparently, unlike women at average risk of ovarian cancer (for whom prophylactic oophorectomy in conjunction with hysterectomy for benign disease may be associated with decreased overall survival; see the review of the study by Parker and colleagues, page 46), women with BRCA mutations may benefit from oophorectomy.

Advantages of prophylactic bilateral salpingo-oophorectomy in this patient population should be discussed with potential surgical candidates, because:

- Women who have a BRCA mutation and who have had bilateral salpingo-oophorectomy were shown to have improved overall and cancer-specific survival.
- In this specific group of BRCA mutation carriers, this study did not demonstrate an increased risk of mortality from cardiovascular disease, osteoporosis, or other causes associated with premature menopause from bilateral salpingo-oophorectomy.

FAST TRACK

Women who have a BRCA mutation may improve their overall and cancer-specific survival with prophylactic oophorectomy

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In BRCA carriers, HRT after oophorectomy does not raise breast cancer risk

Rebbeck TR, Friebel T, Wagner T, et al; for the PROSE Study Group. Effect of short-term hormone replacement therapy on breast cancer risk reduction after bilateral prophylactic oophorectomy in BRCA1 and BRCA2 mutation carriers: the PROSE Study Group. *J Clin Oncol.* 2005;23:7804-7810.

In women with BRCA1 or BRCA2 mutations, the risk of ovarian cancer is staggering (20% to 40% for BRCA1 mutations, 15% to 25% for BRCA2 mutations), and prophylactic bilateral salpingo-oophorectomy is the only strategy proven to significantly reduce risk. A second important benefit for bilateral salpingo-oophorectomy among premenopausal mutation carriers is that the procedure decreases the risk of breast cancer by 50%. In women who have a lifetime risk of breast cancer that is as high as 80%, this benefit is extremely welcome. Current recommendations are for women with BRCA1 or BRCA2 mutations to undergo bilateral salpingo-oophorectomy at age 35 to 40, or when child-bearing is complete.

Yet, for many women in this age group, quality of life is substantially altered when premature menopause kicks in after the surgery. Most ObGyns feel comfortable giving short-term hormone replacement therapy (HRT) after prophylactic bilateral salpingo-oophorectomy to premenopausal women who do not have a history of breast cancer. However, until this study, no data were available that addressed the question of whether short-term HRT affects breast cancer risk.

In a prospective cohort of 462 women, of whom 155 underwent bilateral salpingo-oophorectomy, Rebbeck and colleagues evaluated the risk of developing breast cancer over an average of 3.6 years based on exposure to any type of HRT. In this multicenter study conducted at 13 different institutions in the United States and Europe, they found that women who underwent bilateral salpingo-oophorectomy for a BRCA1 or BRCA2 mutation were more likely to be older, have had children, and were more likely to use HRT. Compared with women who did not have bilateral salpingo-oophorectomy, women who had undergone the procedure and used any short-term HRT (including estrogen, progesterone, or a combination) still had a substantial decrease in breast cancer risk (HR = 0.37; 95% CI, 0.14-0.96).

Practice recommendations

We can now reassure young women who must decide whether to undergo prophylactic bilateral salpingo-oophorectomy to reduce their staggering risks of breast and ovarian cancer: Short-term HRT to address the hot flashes, night sweats, and vaginal dryness associated with premature surgical menopause, first, is clinically reasonable and, second, will not substantially reduce the benefits of bilateral salpingo-oophorectomy for breast cancer risk. ■

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Short-term HRT after prophylactic oophorectomy in women who have a BRCA mutation won't raise their risk of breast cancer

COMING IN AUGUST

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CONTRACEPTION

Philip Darney, MD
University of California-San Francisco

In every issue's **UPDATE**, an expert reviews the decisive studies, emerging clinical issues, and new drugs, devices, and techniques that are changing patient care