■ BY IRA R. HOROWITZ, MD

GYNECOLOGIC CANCERS

- Breast self-exam: Helpful or not?
- HPV vaccine promises cost-effective benefits

OVARIAN CANCER

- HRT increases risk
- Consolidation therapy extends disease-free interval

Gynecologic oncology is a dynamic subspecialty—one with several important recent developments. For example, closer scrutiny of breast self-examination has changed its status from "required" to optional, and greater understanding of cervical carcinoma and its causes is leading to a vaccine for human papillomavirus (HPV) 16/18 in the near future—an achievement likely to be highly cost-effective.

On the ovarian cancer front, data from the Women's Health Initiative suggest an increase in cancer rates in women who take hormone replacement therapy (HRT). In fact, ovarian cancer remains our greatest challenge, since 70% of patients are not diagnosed until they reach advanced stages III and IV, when 5-year survival ranges from 5% to 40%. Fortunately, recent findings suggest consolidation therapy may help extend survival and disease-free intervals.

This update focuses on important studies in each of these areas, highlighting significant progress in understanding, preventing, identifying, and treating gynecologic malignancies.

▪ *Dr. Horowitz is the Willaford Ransom Leach Professor and vice chairman, department of gynecology and obstetrics, and director, division of gynecologic oncology, Emory University School of Medicine, Atlanta, Ga.*

Breast self-examination: Helpful or not?

Hackshaw AK, Paul EA. Breast self-examination and death from breast cancer: a meta-analysis. *Br J Cancer*. 2003; 88:1047–1053.

With 1 in 6 women likely to develop breast cancer, the drive to identify patients with early disease continues apace, especially since survival frequently depends upon it. While mammography remains the gold standard for breast cancer screening, the role of breast self-examination (BSE) is controversial. In May 2003, the American Cancer Society revised its guidelines, changing BSE from a routine to an optional practice. The meta-analysis by Hackshaw and Paul evaluated the effect of BSE on the death rate from breast cancer, reviewing 20 observational and 3 clinical trials on BSE and death or, alternatively, BSE and advanced breast cancer (a surrogate for poor prognosis and increased death rate). They evaluated BSE in women who:

- Practice BSE routinely
- Found tumors during BSE
- Are trained in BSE

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Advantages seen in observational studies likely due to bias and confounding variables. The only trials demonstrating an advantage for BSE were observational studies of breast cancer patients who performed BSE prior to diagnosis. These demonstrated a lower risk of mortality (relative risk [RR], 0.64; 95% confidence interval [CI], 0.56–0.73) and advanced cancer (RR, 0.60; 95% CI, 0.46–0.80).

However, these results are likely caused by bias and confounding. For example, many patients who practiced BSE were younger and of higher socioeconomic status than women who did not. A confounding variable in the observational studies was the presence of slow-growing tumors.

BSE did not lower death rate. No study found a lower death rate in women who detected their breast cancer during BSE (RR, 0.9; 95% CI, 0.72–1.12). Nor did the death rate diminish among women who were trained to perform BSE (RR, 1.01; 95% CI 0.92–1.12), although BSE did appear to prompt many women to seek medical advice. Unfortunately, many studies evaluating the effects of BSE also include mammography, which makes it difficult to isolate effects due solely to BSE.

Clinical implications. Although this meta-analysis supports the American Cancer Society recommendation not to require breast self-examination as a cancer screening tool, I have managed a number of patients who presented with breast masses identified through BSE. Many of these women were low-risk and younger than 30 years. For that reason, I continue to instruct and encourage patients to perform BSE, since it is easily taught and carried out.

I believe BSE helps empower women to take control of their health.

RELATED READING

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Vahabi M. Breast cancer screening methods: a review of the evidence. *Health Care Women Intern*. 2003;24:773–793.

Adding HPV vaccine to cervical cancer screening would be cost-effective

Goldie SJ, Kohli M, Grima D, et al. Projected clinical benefits and cost-effectiveness of a human papillomavirus 16/18 virus. *J Natl Cancer Inst.* 2004;96:604–615.

Because of the link between cervical cancer or dysplasia and HPV infection, HPV vaccination in childhood or adolescence would virtually eradicate cervical cancer. It also would be cost-effective, compared with the cost of screening, evaluating, and treating dysplasia and cervical cancer.

In 2002, Koutsky et al[1] reported a randomized, prospective trial of an HPV-16 vaccine, in which they found vaccination to be 100% effective (95% confidence interval [CI], 90–100; $P<.001$), with an incidence of persistent HPV-16 infection of 0 per 100 woman-years in vaccinated women versus 3.8 per 100 woman-years among controls. At the time of its publication, this trial was the largest ever conducted of an HPV vaccine, with 2,392 women enrolled (1,198 in the placebo group and 1,194 in the vaccine group).

Following the Koutsky trial, Goldie and colleagues reported on a computer-based model to evaluate the efficacy and cost of vaccinating patients with an HPV 16/18 vaccine. Using the Markov model, they simulated HPV infection and carcinogenesis. However, rather than evaluate the cost-effectiveness of the vaccine as a single modality, they added it to current cytologic testing, evaluating screening intervals of 1 to 5 years with conventional and liquid-based smears.

The most cost-effective screening strategy was vaccination at age 12 and cytologic screening every 3 years beginning at age 25. Using this approach, the lifetime risk of cervical cancer would be reduced by 94% compared with no screening—a spectacular improvement.

HPV vaccines will become available in the next several years, at which time we will need to determine their appropriate use in

industrialized nations, such as the United States, where about 3,900 cervical cancer deaths will occur this year, as well as in developing countries. Worldwide, roughly 500,000 women die of the disease each year. In developing countries, the vaccine would decrease the incidence of dysplasia by more than 50%, even if used as a single modality.

Clinical implications. Although most dysplasias and carcinomas are related to HPV 16/18, it is imperative that we continue to screen to rule out infection with other high-risk subtypes. Eventually, a polyvalent vaccine may enable us to vaccinate for all known high-risk subtypes.

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HRT increases risk of ovarian cancer

Anderson GL, Judd HL, Kaunitz AM, et al. Effects of estrogen plus progestin on gynecologic cancers and associated diagnostic procedures: the Women's Health Initiative randomized trial. *JAMA*. 2003;290:1739–1748.

The Women's Health Initiative has produced the single largest randomized, prospective trial comparing estrogen, continuous estrogen-progesterone, and placebo. Recent findings from this population include an increased risk of breast cancer, heart disease, dementia, and vascular thrombosis with HRT use.

Now Anderson and colleagues have reported on the association between gynecologic cancers and HRT—specifically, the estrogen-progestin combination. In the randomized, double-blind study involving 16,608 postmenopausal women, participants were given 0.625 mg of conjugated equine estrogens and 2.5 mg of medroxyprogesterone acetate (n = 8,506) or placebo (n = 8,102), and the main outcome measure was invasive cancer of the ovary or endometrium.

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After an average follow-up of 5.6 years, Anderson et al found 32 cases of invasive ovarian cancer, 58 cases of endometrial cancer, 1 case of non-endometrial uterine cancer, 13 cases of cervical cancer, and 7 cases of other gynecologic cancers.

Compared with controls, women taking HRT experienced a significantly increased incidence of ovarian cancer, with a hazard ratio of 1.58 (95% CI, 0.77–3.24). For endometrial cancer, the hazard ratio was 0.81 (95% CI, 0.48–1.36). The groups did not differ significantly in regard to the other cancers.

More endometrial biopsies. Another important finding from this study is the greater need for endometrial biopsies among women taking HRT (33% versus 6%; $P < .001$).

Other trials also have reported an increased risk of ovarian cancer with HRT use, as well as the decreased risk of endometrial cancer.

Because of the greater risk associated with HRT, indications for it have changed. Now most HRT users are young and take the therapy to relieve vasomotor symptoms. These women should be counseled about the risks outlined in the Women's Health Initiative, as well as the importance of endometrial biopsies to evaluate any abnormal bleeding.

Clinical implications. In the next 5 years, alternative therapies such as selective estrogen receptor modulators are likely to replace HRT. Until then, I will continue to prescribe HRT, but only in symptomatic women for a period of less than 5 years.

RELATED READING

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Consolidation therapy extends disease-free interval

Markman M, Liu PY, Wilczynski S, et al. Phase III randomized trial of 12 versus 3 months of maintenance paclitaxel in patients with advanced ovarian cancer after complete response to platinum and paclitaxel-based chemotherapy. Southwest Oncology Group and Gynecologic Oncology Group Trial. *J Clin Oncol*. 2003;21:2460–2465.

Standard therapy for ovarian cancer consists of 6 courses of a platinum (cisplatin or carboplatin) and taxane (paclitaxel or docitaxel) regimen. Following such therapy, second-look laparotomy or laparoscopy once was widely performed. However, that strategy has not been shown to increase survival: 50% of second looks for suspected ovarian cancer are pathologically positive, while an additional 25% are pathologically positive within 3 years.

For this reason, other ways of extending the disease-free interval and improving survival are under investigation. The study by Markman and colleagues focuses on consolidation therapy, which is treatment administered after a complete pathologic or clinical response. Whole abdominal radiation, intraperitoneal radioactive phosphorus (^{32}P), and chemotherapy have been evaluated.

In this study, the Gynecologic Oncology Group and Southwest Oncology Group compared 3 versus 12 months of maintenance paclitaxel in patients who had a complete response to platinum/paclitaxel chemotherapy. Two arms were established: one giving paclitaxel 175 mg/m^2 over 3 hours every 28 days for 3 cycles, and another extending this regimen to 12 cycles.

The median progression-free survival times were 21 and 28 months in the 3- and 12-month arms, respectively. *P* values for the adjusted Cox model analysis and unadjusted log-rank test were .0023 and .0035, respectively, with the 12-month arm having superior results. The Cox model-adjusted 3-cycle versus 12-cycle progression hazard ratio was estimated to be 2.31 (99% CI, 1.08–4.94). Because the protocol recommended early termination of the trial at a cutoff *P* value of .005, the trial was discon-

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tinued and all women were given the opportunity to receive 12 courses of paclitaxel.

Although these results are statistically significant, the 5-year survival and disease-free intervals are not available. Therefore, the role of consolidation chemotherapy with agents such as paclitaxel—which is not without side effects—needs further investigation before it can become the standard of care.

Clinical implications. I present the option of consolidation chemotherapy to all patients, encouraging them to participate in clinical trials of the therapy. If a trial is not available, I give the patient the option of receiving 12 cycles of paclitaxel off protocol or continued observation. I also discuss current data, including pros and cons, with the patient prior to initiating consolidation therapy. ■

RELATED READING

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Dr. Horowitz reports no financial relationships relevant to this article.

Watch for UPDATE ON CONTRACEPTION

By Patricia J. Sulak, MD
Professor
Department of Obstetrics and Gynecology
Texas A&M College of Medicine

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