



Karen H. Lu, MD
Associate Professor,
Department of Gynecologic
Oncology, University
of Texas M. D. Anderson
Cancer Center

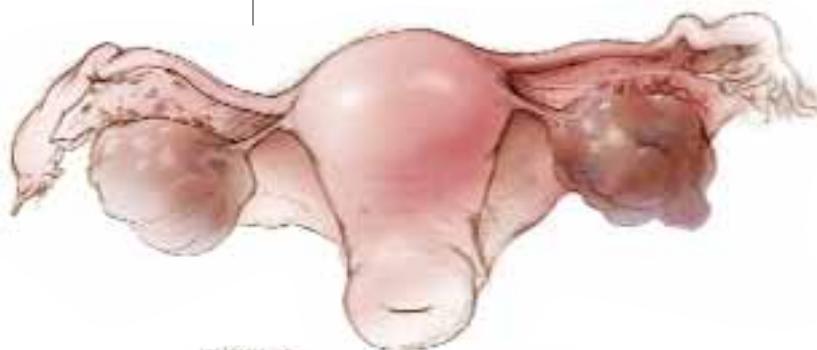
GYNECOLOGIC CANCER

Distinctive symptoms flag *early* ovarian cancer ... Where's the blood test? ... Don't fail to counsel risk-reducing BSO ... Serial histologic sectioning is vital

This *Update* reviews recent findings of importance to obstetricians and gynecologists. Late detection of ovarian cancer is still the main reason for the high mortality rate of the most deadly of the gynecologic cancers. Approximately 22,200 women will be newly diagnosed in the United States this year, and there will be 16,210 deaths. Since ovarian cancer is still initially

detected in its advanced stages in more than 70% of cases, when cure rates are low, early detection and prevention remain our greatest challenge. The gynecologic oncologist's opportunity to successfully treat malignancy depends on early detection, and therefore physicians providing primary care for women are our firstline guardians.

"Silent killer" may not be so stealthy



STERILIS
CYSTADENOCARCINOMA

Goff BA, Mandell LS, Melancon CH, Muntz HG. Frequency of symptoms of ovarian cancer in women presenting to primary care clinics. *JAMA*. 2004;291:2705-2712.

Women ultimately diagnosed with malignant masses had a triad of symptoms, as well as more recent onset and greater severity of symptoms than women with benign masses or no masses. A diagnostic workup employing transvaginal ultrasound and CA-125 should be considered when a woman says she has these symptoms.

Ovarian cancer is not a silent disease. It was believed to be a "silent killer" because it was thought to be asymptomatic until a woman had very advanced disease. However, Goff and colleagues, in a previous study, found that 95% of women with ovarian cancer had had symptoms prior to diagnosis—and that

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the type of symptoms was not significantly different, whether disease was early stage or late stage.

This new study aimed to identify the frequency, severity, and duration of symptoms typically associated with ovarian cancer, by comparing symptoms reported by different groups of women. Symptoms reported by women presenting to primary care clinics were compared with symptoms reported by a group of 128 women with ovarian masses. Importantly, women were surveyed about their symptoms before undergoing surgery, and before they had a diagnosis of cancer or benign disease.

Main findings:

- **A triad of symptoms**—abdominal bloating, an increase in abdominal girth, and urinary symptoms—occurred in 43% of women found to have ovarian cancer, but in only 8% of women who presented to a primary care clinic.
- **The frequency and duration of symptoms** in women with ovarian masses were more severe in the women with malignant masses, but were of a similar type regardless of whether the mass was benign or ovarian cancer.
- **Onset of symptoms** was more recent in women with ovarian cancer than in the control group.

Listening carefully and evaluating the severity, frequency, and duration of symptoms, especially abdominal bloating, an increase in abdominal girth, urinary symptoms, and abdominal pain, is all-important.

Ovarian cancer should be included in the differential diagnosis when a woman says she has these symptoms.

I found it interesting that symptoms with a more recent onset may be more consistent with ovarian cancer.

In an ideal world, a simple blood test with an absolute cutoff, with perfect sensitivity and specificity, would identify ovarian cancer at its earliest stages. However, until such a test exists, primary care physicians and ObGyns should continue to put weight on the symptoms the patient communicates.

Transvaginal ultrasound and CA-125

Consider performing a diagnostic workup employing transvaginal ultrasound and CA-125 measurement in women presenting with these complaints.

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Whatever happened to the ovarian cancer blood test?

Ransohoff DF. *Lessons from controversy: ovarian cancer screening and serum proteomics*. *J Natl Cancer Inst*. 2005;97:315–319.

- Science is still seeking the Holy Grail—a blood test for early detection of ovarian cancer.

When Petricoin et al reported in 2002 that a serum proteomic profiling test had nearly 100% sensitivity and specificity, the media trumpeted the phenomenal news. The public's hopes soared when news articles reported that a company would soon begin offering the test.

Patients brought in these reports to their ObGyns and asked for the test.

Plans to introduce a commercial screening test by early 2004 were delayed, however, due to FDA concerns about its reliability. The reasons for claims, plans, and delays were reported in both professional journals and the lay press, but details on the “question about whether the approach of discovery-based serum proteomics can accurately and reliably diag-

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Triad of symptoms found in *early* ovarian cancer

- Abdominal bloating
- Increased abdominal girth
- Urinary symptoms

nose ovarian cancer—or any cancer—have not been resolved,” Dr. Ransohoff explains in this thoughtful 2005 essay.

He describes in a simple and straightforward way the requirements of reproducibility, and what these new technologies must demonstrate. He concludes that serum proteomic profiling for the early detection of ovarian cancer has not demonstrated the reproducibility required of a clinical test.

“Chance and bias may cause erroneous results and inflated expectations in the kind of observational research being conducted in several ‘-omics’ fields to assess molecular markers for diagnosis and prognosis of cancer. To realize the potential of new -omics technology will require appropriate rules of evidence in the design, conduct, and interpretation of the clinical research,” writes Dr. Ransohoff.

While proteomic profiling clearly has

promise, clinicians should insist that initial studies be validated

What to tell patients. I explain that the test appeared promising, and therefore was of great interest, but the FDA did not allow it to be put on the market because of insufficient evidence that the test consistently defines whether cancer is or is not present. Since either a negative or positive test would have profound effects, accuracy is an absolute requirement.

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Petricoin EF, Ardekani AM, Hitt BA, et al. Use of proteomic patterns in serum to identify ovarian cancer. *Lancet.* 2002;359:572-577.

Don't hold back from counseling risk-reducing BSO when indicated

Metcalf KA, Lynch HT, Ghadirian P, et al. The risk of ovarian cancer after breast cancer in BRCA1 and BRCA2 carriers. Gynecol Oncol. 2005;96:222-226.

■ Counsel women with breast cancer who are BRCA1 or BRCA2 mutation carriers to consider prophylactic salpingo-oophorectomy after childbearing is complete. Tamoxifen and chemotherapy do not lower risk.

Obgyns should encourage young women with breast cancer or women with a strong family history of breast and/or ovarian cancer to undergo genetic testing.

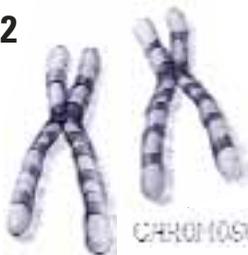
Women with breast cancer who are found to be BRCA1 or BRCA2 mutation carriers should be counseled by their gynecologists to consider prophylactic BSO after childbearing is complete. Even though these women's greatest concern may be breast cancer recurrence, gynecologists should advise these women that they are

also at risk for ovarian cancer, and that they can substantially decrease their risk by undergoing risk-reduction surgery. BRCA1 mutation carriers have up to an 80% lifetime risk of breast cancer and up to a 50% lifetime risk for ovarian cancer.

Recent data support intervention to decrease risk: BSO decreases risk of ovarian cancer by more than 90%, and decreases risk of breast cancer by 50% in BRCA1 or BRCA2 mutation carriers. Metcalf et al examined women with a BRCA1 or BRCA2 mutation and a history of stage I or II breast cancer, and found that 10% developed an ovarian cancer, a fallopian tube cancer, or a peritoneal cancer. The median time was 8.1 years from the development of breast cancer to the development of ovarian cancer. The cumulative risk of developing ovarian cancer after breast cancer was

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BSO lowers risk of ovarian cancer by 90% and breast cancer by 50% in BRCA1 or BRCA2 mutation carriers



12.7% for BRCA1 mutation carriers and 6.8% for BRCA2 mutation carriers.

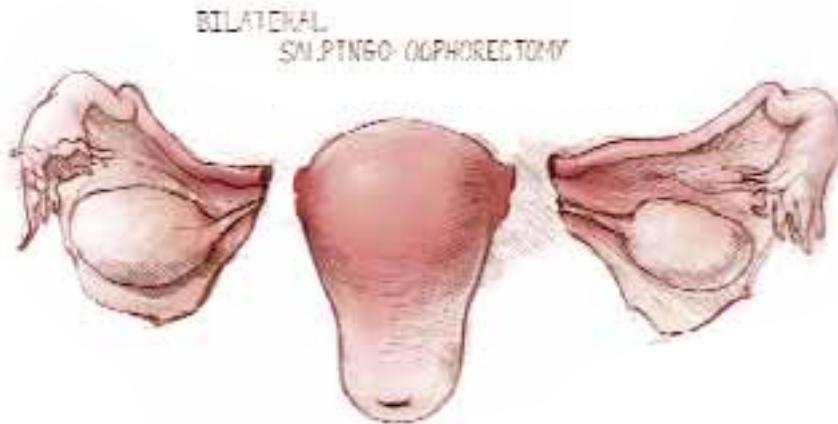
Tamoxifen or chemotherapy did not change this risk. The authors concluded that BSO could have prevented at least 43 to 46 ovarian cancers.

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Kauff ND, Satagopan JM, Robson ME, et al. Risk-reducing salpingo-oophorectomy in women with a BRCA1 or BRCA2 mutation. *N Engl J Med.* 2002; 346:1609-1615.

Serial histologic sectioning is vital for detecting occult malignancy



Powell CB, Kenley E, Chen LM, et al. Risk-reducing salpingo-oophorectomy in BRCA mutation carriers: role of serial sectioning in the detection of occult malignancy. *J Clin Oncol.* 2005;23:127-132.

■ A specific 4-step protocol for salpingo-oophorectomy and pathologic examination increased the number of occult malignancies identified.

Is a risk-reducing BSO any different from a BSO for benign reasons? The evidence is a resounding YES. Given the strong data supporting prophylactic BSO in women with BRCA1 or BRCA2 mutations, ObGyns are increasingly called upon to perform this procedure. Current recommendations are to offer surgery to mutation carriers after childbearing or in their mid- to late 30s and early 40s. A number of studies have discovered that carriers who undergo risk-reducing BSO are at increased risk for occult malignancies already existing in the ovaries and fallopian tubes.

These studies recommend use of a specific surgical approach and pathologic examination of specimens.

Powell et al found an increased number occult malignancies with this strategy:

1. Complete removal of ovaries and fallopian tubes
2. Serial histologic sectioning of both ovaries and fallopian tubes
3. Peritoneal and omental biopsies
4. Peritoneal washings for cytology

Of 67 procedures, 7 (10.4%) occult malignancies were discovered: 4 in the fallopian tubes and 3 in the ovaries. Six of the occult malignancies were microscopic.

Surgically, the entire ovary and fallopian tube should be removed. I perform washings and carefully look at the pelvis and paracolic gutters for small-volume disease.

Most importantly, ObGyns need to speak with the pathologist. For most *benign* cases in which the ovaries and fallopian tubes look grossly normal, pathologists take a *single* representative section of each ovary and fallopian tube for histologic diagnosis. However, in these *high-risk* cases, *complete* serial sectioning of ovaries and fallopian tubes is absolutely necessary to rule out microscopic cancer. Removal of the uterus should be based on other indications. ■

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Occult cancer may already exist in the ovaries or fallopian tubes when risk-reducing BSO is performed