ELISA test marks 35 years [PAGE 30]

Health & Science

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OVARIAN CANCER

Detecting a killer

Sharpened clinical skills are called for in diagnosing ovarian cancer early, when it's most curable.

STORY BY SUSAN J. LANDERS

It's a given that ovarian cancer is difficult to detect. The almond-size ovaries are deep within the pelvis, and textbooks written just 10 years ago say this disease has no symptoms. But new studies indicate that it often does announce itself, and women and their physicians might hear it if they listened.

Many women, for instance, don't realize that abdominal swelling and pain, fatigue and urinary problems could be symptoms of ovarian cancer. This oversight often proves fatal.

An estimated 22,000 U.S. women were diagnosed with ovarian cancer last year, and 16,000 died from it, making it the most lethal cancer of the female reproductive system, says the National Cancer Institute.

4 out of 10 women with ovarian cancer described symptoms 4 months to a year before diagnosis.

Earlier diagnosis is a life-or-death matter. Almost 70% of women with ovarian cancer are not diagnosed until the disease is in stages III or IV. If detected at stage I, the five-year survival rate is 90%. If caught in stages III or IV, that rate drops to 15% or 20%.

Oncologists who treat these women encourage a heightened level of awareness from primary care doctors and female patients, particularly those past menopause. They urge consideration of ovarian cancer when a woman complains of sudden, serious and frequent symptoms.

"If you don't even think about it, how can you diagnose it?" asked David Fishman, MD, director of gynecologic oncology at New York University.

Granted, the complaints are often vague and could be triggered by any number of conditions, from irritable bowel syndrome to colon cancer. But more experts are promoting early evaluation through a pelvic exam, transvaginal or abdominal ultrasound and a blood test for a protein biomarker called CA-125.

"I take care of ovarian cancer patients all the time," said Lloyd Smith, MD, PhD, professor and chair of obstetrics and gynecology at University of California, Davis, Medical Center. "It's really, really frustrating to hear one after

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Women's health: risks and realities

THREE MAIN TYPES OF OVARIAN TUMORS

Epithelial ovarian tumors. Most common form; derived from the cells on the surface of the ovary
Germ cell tumors. Derived from egg-producing cells within the body of the ovary; rare, occurring primarily in children and teens
Sex cord stromal tumors. Also rare; formed from the ovary's stromal component or matrix

SOURCE: JOHNS HOPKINS PATHOLOGY

POSSIBLE RISK FACTORS FOR EPITHELIAL OVARIAN CANCER

- One or more first-degree relatives with ovarian and/or breast cancer
- A personal history of breast, endometrial and/or colon cancers
- A history of infertility or the use of fertility drugs
- Ashkenazi Jewish heritage and a family history of breast and/or ovarian cancer
- A mutation in the BRCA1 or BRCA2 gene

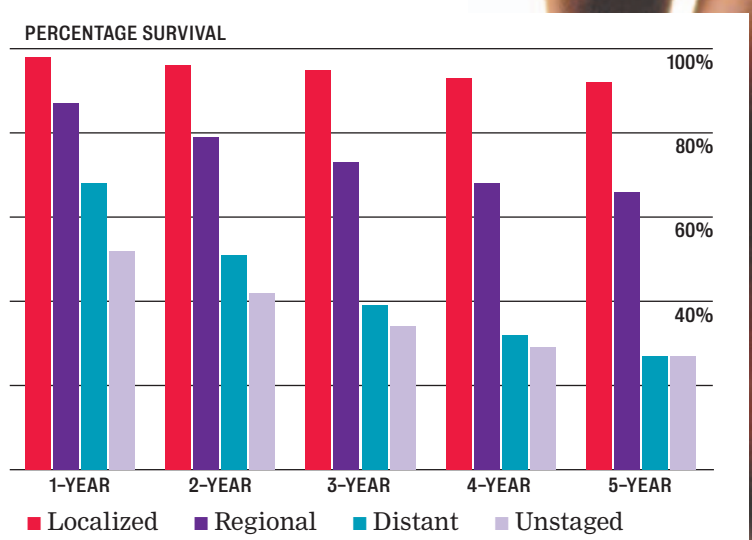
SOURCE: MD ANDERSON CANCER CENTER

FACTORS ASSOCIATED WITH A DECREASED RISK OF OVARIAN CANCER

- Using oral contraceptives
- Having and breastfeeding children
- Having a bilateral tubal ligation or hysterectomy
- Having a prophylactic oophorectomy

SOURCE: THE NATIONAL CANCER INSTITUTE

RELATIVE SURVIVAL RATES BY STAGE OF DIAGNOSIS FOR OVARIAN CANCER



SOURCE: THE NATIONAL CANCER INSTITUTE

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another saying, 'I've been having pain for months, and they did this and that, and no one ever did a pelvic exam and no one ever did anything to figure [it] out.' "

In a study published last fall in *Cancer*, Dr. Smith and his colleagues found that four in 10 women with the disease had described symptoms to doctors at least four months — and as long as a year — before diagnosis.

Based on these findings, Dr. Smith offers a basic message. Heightened attention should be paid to women older than 50 who have recently developed multiple symptoms such as abdominal pressure, pain, swelling and bloating. "For those people, I would definitely think about ovarian cancer right up front."

Index of suspicion

Barbara Goff, MD, director of the University of Washington's Division of Gynecological Oncology, is working on an index of symptoms similar to the set described above to help primary care physicians determine whether to refer patients for additional analysis. This effort might help address a key issue.

"If you talk to women in the survivor community, there is a lot of hostility and anger toward health care providers," she said. "Many had symptoms, and they went in repeatedly but were told there was nothing wrong."

In 2000, Dr. Goff and colleagues surveyed 1,725 women in 46 states and four Canadian provinces who were diagnosed with ovarian cancer and found that nearly 90% reported having one or more symptoms, often several months before diagnosis.

Although 55% of the women were correctly diagnosed within two months of showing symptoms, 15% were told they had irritable bowel disease, 12% were told the symptoms were due to stress and 15% were told there was nothing wrong.

Among her current patients, Dr. Goff finds about half have had symptoms, but the rest did not. Those without symptoms were diagnosed promptly but usually with advanced disease.

Though finding this cancer at earlier stages seems out of reach, it is possible to do better, according to Judith Wolf, MD, medical adviser to the National Ovarian Cancer Coalition's Advisory Board. She urges earlier sonograms. "People think nothing of getting CT scans, colonoscopies and upper endoscopies and all of these other invasive, expensive tests," she says, so why not add a pelvic ultrasound?

Most women who arrive at Dr. Wolf's office haven't had a rectal exam, which could provide an important clinical clue, because the ovaries often sit behind the uterus, she said. The increasing weight of many patients, though, is making physical detection difficult. "Imagine trying to feel a small ovary through 6 inches of fat. It's hard. Even if you know a mass is there, it's hard to feel it."

But earlier detection also can come from just listening. "What it means is a dialogue between physicians and patients," said Mary Daly, MD, PhD, senior vice president for population science at Fox Chase Cancer Center in Philadelphia. "Women need to feel empowered that they have the right to go and complain about these symptoms and not be told, 'It's all in your head.' " If women are experiencing unusual symptoms that don't disappear, they should be taken seriously.

Edward Trimble, MD, who leads gynecologic cancer therapeutics at the National Cancer Institute, advises primary care physicians to ask about family cancer history. BRCA2 and, especially, BRCA1 mutations put women at greater risk of ovarian cancer as well as breast cancer.

Instances of hereditary nonpolyposis colorectal cancer also increases a woman's risk for ovarian as well as other cancers. "It's very important ... to explore family history, and if someone has a suspicious family history, she should be referred to a specialized center in cancer genetics," Dr. Trimble said.

Screening difficulties

Because ovarian cancer is relatively rare and its early symptoms are vague, a more accurate means of identification is needed. Both the CA-125 test and transvaginal ultrasound generate so many false positives they are not recommended for screening the general population.

A CA-125 can miss half of the women with early ovarian cancer, and several benign conditions can cause an elevation of CA-125 levels, Dr. Trimble said. "We use the CA-125 and the ultrasound, because that's all we have."

A study last fall in the *American Journal of Obstetrics and Gynecology* also pointed up the tests' limitations. It examined whether screening with transvaginal ultrasound or CA-125 decreases ovarian cancer mortality in women ages 55 to 74 and found numerous false positives.

Of nearly 29,000 healthy women screened, 1,338 had an abnormal ultrasound and 402 had an abnormal CA-125 blood test. Thirty-four had abnormal results in both. Among the women with abnormal test results, 29 tumors were detected, 20 of which were invasive cancers.

Women with abnormal results in one or both screening tests underwent several diagnostic procedures to determine if cancer was present, including 570 who had a surgical procedure. Thus, said the authors, 541 women underwent unnecessary surgery.

The results show that even though ovarian cancer is often fatal and patients and doctors want ways to uncover it at an earlier, more curable stage, ultrasound and CA-125 cannot be recommended for widespread use, concluded lead author Saundra Buys, MD, professor of internal medicine at the University of Utah's Health Sciences Center in Salt Lake City.

Dr. Buys' trial is ongoing, as are several others. "We're still waiting for the breakthrough," Dr. Smith said. "Every few years, there is something [new], like proteomics or transvaginal ultrasound, but nothing is perfect."

John van Nagell, MD, who guides the 18-year Ovarian Cancer Screening Program at the University of Kentucky, has screened more than 25,000 women using transvaginal ultrasound. This group includes women older than 50 and those who are at least 25 and have a documented family history of the disease.

Dr. van Nagell has found that 35 had ovarian cancer, with 80% detected at stage I. "I do think we need to study detection very carefully," he said. "It's worth it. Every year we build something into the algorithm."

Meanwhile, Dr. Fishman believes the emerging understanding of proteomics could help. "The future ... is going to change dramatically, because we have new protein identification technologies that we have never had in the history of medicine."

In addition, Dr. Fishman said, imaging is poised to become a more exacting tool for spotting suspicious changes. He and other researchers at NYU are pioneering contrast sonography that will pick up microvascular changes to allow clinicians to find cancer before a mass is visible.

But until technology can take over, physicians will need to keep their clinical detection skills sharp. What can primary care physicians do? The answer is simple, Dr. Fishman said. "[They can] take a comprehensive history, perform a physical and a thorough gynecologic exam, listen to patients' concerns about possible symptoms and ask themselves if they could mean ovarian cancer. If there is any suspicion, the test to use is ultrasound, vaginal or abdominal, to examine the ovaries." Any suspicious masses, he noted, should trigger a referral to a gynecologic oncologist. ◆

A challenging diagnosis

Recent studies indicate a majority of women with ovarian cancer complained to physicians of symptoms shared with benign diseases before diagnosis. Experts say if symptoms are of recent onset and more severe or frequent than expected, they should be investigated.

The most common to watch for:

- Back pain
- Fatigue
- Bloating
- Constipation
- Abdominal pain
- Urinary problems

◄ **Mucinous carcinoma of the ovary accounts for approximately 10% of all ovarian cancers and is relatively common.**

WEBLINKS

http://www.cancer.org/docroot/cri/cri_2_1x.asp?dt=33 *American Cancer Society on ovarian cancer* **http://www.cancer.gov/cancertopics/types/ovarian** *National Cancer Institute on ovarian cancer* **http://www.gildasclub.org/** *Gilda's Club Worldwide* **http://www.ovarian.org/** *National Ovarian Cancer Coalition*

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