

FEATURE STORY

Warning Signs

BY MELISSA KNOPPER

Paying attention to early symptoms of ovarian cancer—among both doctors and patients—may give a voice to the "silent killer," but some advise caution.

Before she was diagnosed with stage 1 ovarian cancer at age 44, Pam Faerber noticed pain in her back and abdomen and a bloated stomach. "Like so many of us women do, I started talking about it to my hairdresser," Faerber recalls. A month later when the busy Indianapolis businesswoman went to the internist her hairdresser recommended, the doctor said it was probably menopause. Faerber, now a 14-year survivor, wishes she had asked for a second opinion right then. Instead, she waited four months until she was doubled over with pain. "I knew something was wrong with my body, but I was not proactive," she says.

At the time, Faerber thought she had appendicitis. She never considered ovarian cancer as the root of her pain. "It's so soundly engrained in the medical field—and among women—as the 'silent killer,' " says Faerber, founding member of the Ovarian Cancer National Alliance.

In fact, most women are diagnosed at a late stage when they only have a 20 to 30 percent chance of surviving five years, according to the American Cancer Society. By contrast, patients with cancer that is confined to the ovary can have a greater than 90 percent survival rate, but only about 20 percent of cases are found at such an early stage. Overall, the ACS estimates 22,000 women will be diagnosed with ovarian cancer in 2007, and 15,000 will die of the disease.

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—Pam Faerber



Pam Faerber at home with her horses. Photo by Charles A. Farris

New research shows ovarian cancer does offer some clues if we are tuned in enough to watch and listen for them, but the vagueness of the symptoms worry some experts. Even so, ovarian cancer advocates like Faerber are putting the focus on symptoms, and hoping to change statistics for the better. “We need a cure and we need better screening tests,” says Faerber, who also serves on Fox Chase Cancer Center’s Patient Advocate Research Team. “In the interim, we need to get the facts straight about symptoms so we can quit finding these women in such late stages.”

Symptoms Debate

The studies, by Barbara A. Goff, MD, a University of Washington gynecologic oncologist, showed a pattern: Women noticed a similar set of symptoms before being diagnosed with ovarian cancer. “What we found was ovarian cancer wasn’t silent,” Dr. Goff says. “Ninety-five percent of women have symptoms.”

This cluster of symptoms is clearly spelled out in a consensus statement released in June 2007 by several groups, including the Gynecologic Cancer Foundation, the Society of Gynecologic Oncologists, and the American Cancer Society. The consensus statement says women should watch for the following symptoms: abdominal bloating or increased abdominal size; pelvic pain or abdominal pain; urinary frequency or urgency; and difficulty eating (feeling full too quickly).

“You’ll notice we didn’t include fatigue in the statement because although a lot of survivors have fatigue, it’s still not predictive of having ovarian cancer,” Dr. Goff says. Although the symptoms themselves may seem vague, she points out that if the symptoms are new and unusual, and if they persist almost every day or every other day for more than two weeks, the guidelines encourage women to see a doctor to discuss the possibility of ovarian cancer.

View Illustration: [How Ovarian Cancer Causes Symptoms](#)

Dr. Goff’s research showed physicians frequently dismissed women who sought help for ovarian cancer symptoms. Instead, she says, the women were told they

were suffering from irritable bowel problems or some other illness. One-third of the women Dr. Goff surveyed were given medication for a condition other than ovarian cancer. “There clearly was a problem with this whole process,” she says. (Dr. Goff talks about the consensus statement in this issue’s [Speaking Out](#).)

Ovarian cancer advocates, who have been pushing for such a statement for years, are calling it a victory. Now, women can be armed with this information, so they won’t be put off when they go to the doctor’s office for help, says ovarian cancer survivor Karen Mason, 55. “Our hope is this will lead to earlier detection and save lives,” she says.

Mason, an intensive care nurse, experienced numerous symptoms—abdominal pain, lower back ache, and severe fatigue—before she was diagnosed at age 49 with stage 3 ovarian cancer. “I always had a crampy feeling in my pelvis, even when I wasn’t having my period,” she says. Like Faerber, she figured it was just menopause. “If I had seen this list of symptoms, I probably would have been diagnosed sooner,” Mason says.

Since there are no good screening tests for ovarian cancer, Dr. Goff believes it makes sense to view symptoms as a sort of early biomarker. It’s a first step—a way to make the diagnosis earlier, she explains. “Most people who have these symptoms are not going to have ovarian cancer, just like most breast lumps are benign,” Dr. Goff says. “But it’s important to take them seriously and work them up.”

But others wonder if the consensus statement will actually have an impact on survival rates. “It raises the level of consciousness and encourages women to at least ask about the possibility of ovarian cancer,” says Beth Karlan, MD, director of the Women’s Cancer Research Institute and the Gilda Radner Hereditary Cancer Detection Program at Cedars-Sinai Medical Center in Los Angeles. “Will it save lives? That remains to be proven.”

Scientists are still uncertain, for example, how quickly ovarian cancer progresses from an early to advanced state. By the time women notice symptoms, it may be too late to make an early diagnosis, says J. Tate Thigpen, MD, director of the division of medical oncology at the University of Mississippi Medical Center in Jackson.

“The symptoms in the consensus statement are vague and they are usually associated with advanced disease,” Dr. Thigpen says. “I personally think emphasizing the symptoms is going to cause a lot of anxiety, and a lot of work-ups that won’t necessarily lead to an early-stage ovarian cancer diagnosis.”

Other physicians have expressed concern the statement could lead to unnecessary and expensive testing, and even to unneeded surgery and its resulting complications. Since most women who visit the doctor asking about these symptoms will not have ovarian cancer, it could also lead to a lot of waiting and worrying, says ACS President Richard Wender, MD, who chairs the Department of Family and Community Medicine at Thomas Jefferson University Hospital in Philadelphia.

On the positive side, Dr. Wender says, more patients might find help for health conditions besides ovarian cancer that they might otherwise have ignored. “If they come to their clinicians and get reassurance, that’s not so bad,” Dr. Wender says.

“If it contributes to health care costs, that’s not so awful [because] so does a late-stage diagnosis.”

Getting the Word Out

Despite the controversy, activists are busy raising awareness about the symptoms statement. In September, the 21 organizations of GCF’s Allied Support Group gathered to plan a strategy.

“We want to distribute the consensus guidelines to family practice doctors, nurse practitioners, and nurses so they will start to think of ovarian cancer if patients present with these symptoms,” says Ronald Alvarez, MD, GCF’s advocacy chair and executive committee member who directs the Division of Gynecology at the University of Alabama at Birmingham. The groups also will distribute copies of the consensus statement to members of professional societies like the American Society of Obstetricians and Gynecologists.

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Next, the groups would like to develop another document that explains what evaluations doctors should consider when faced with a patient with potential ovarian cancer symptoms.

“It’s going to be challenging because every primary care physician sees a large number of people who have common symptoms, such as belly pain,” Dr. Wender says. “There’s hope this research and the guideline will improve our ability to pick out that one woman who has ovarian cancer from the larger group.”

Debbie Saslow, PhD, director of breast and gynecologic cancers at ACS, predicts a statement on diagnosis should be available in about a year. Any kind of extra awareness will help, advocates say, since ovarian cancer is curable at an early stage.

The process starts with a pelvic exam. If the gynecologist feels a suspicious growth, a transvaginal ultrasound may be the next step. From there, physicians might order a CT (computed tomography) scan or a CA-125 blood test. The test can signal the presence of ovarian cancer cells, but it can also be elevated because of normal causes, such as menstrual changes.

Treating the Disease

If all of these tests show strong signs of ovarian cancer, exploratory surgery may be the next step. Surgery is critical in determining a woman's odds of survival, experts say, because that's when the stage is determined. And staging typically determines the type of treatment that will follow, Saslow says.

A 2006 study published in the *Journal of the National Cancer Institute* found women who had surgery performed by a gynecologic oncologist—a doctor who specializes in diagnosing and treating reproductive cancers—had a 24 percent higher survival rate than those who went to a general surgeon. “The survival is better because the staging is more accurate,” Saslow says.

Both Faerber and Mason say they had no idea how important it was to have the surgery performed by a specialist when they were diagnosed. But they are grateful they were referred to the right type of surgeon.

“Ovarian cancer can look like a bunch of Rice Krispies scattered around your abdomen,” Mason says. If you leave even a tiny trace, the cancer can return, she adds. Mason put her trust in a skilled gynecologic oncologist, and six years later, she's still cancer-free.

During the first surgery, a physician looks for the extent of the cancer, Dr. Thigpen says. If the tumor stays on one or both ovaries, it's stage 1 (low risk of recurrence). If the tumor spreads outside the ovary, it's stage 2. When cancer cells and fluid show up in the abdomen, or if the cancer spreads to other parts of the body, such as the lymph nodes, then the patient has stage 3 or 4 ovarian cancer (high risk of recurrence).

For low-risk stage 1 or 2, Dr. Thigpen may recommend only surgery and close follow-up. For stage 3 or 4, the standard treatment is surgery and chemotherapy with Taxol (paclitaxel) and carboplatin. The drugs are most often given through an I.V., with six cycles once every three weeks.

Usually, patients can tolerate Taxol and carboplatin without too many side effects, Dr. Thigpen says. Some women feel numbness and tingling in their hands and feet as a side effect of Taxol. To prevent peripheral neuropathy, Dr. Thigpen usually lengthens the amount of time they receive their Taxol infusion. Other agents with a proven benefit in ovarian cancer include Doxil (doxorubicin), Hycamtin (topotecan), and Gemzar (gemcitabine).

For advanced ovarian cancer cases, physicians may deliver chemotherapy directly into the abdominal cavity through a catheter. Researchers are still refining this technique, called intraperitoneal chemotherapy. Studies show IP therapy does prolong survival in ovarian cancer, but is extremely hard on patients.

New York cancer survivor Carmen Diaz did her best to tolerate IP therapy, but it was too much. She was given IP cisplatin, which immediately made her vomit. “I was so sick by the third day, we had to call 9-1-1,” Diaz says. The cisplatin damaged her kidneys and she had to be hospitalized for two weeks. Diaz had only one round of the scheduled four rounds of IP therapy.

“We're going to continue to evaluate this,” Dr. Thigpen says. “We're looking at ways to give the IP therapy with fewer side effects.” Two options include decreasing the dose of cisplatin and substituting carboplatin for cisplatin, he

says, both of which must be tested to determine if the efficacy is maintained.

New Approaches

While the initial therapy can be effective, at least 70 percent of ovarian cancer patients face recurring disease. So oncologists are always looking for better tools, says Robert L. Coleman, MD, director of clinical research in the department of gynecologic oncology at M.D. Anderson Cancer Center in Houston.

Targeted agents are among the most promising new therapies in the pipeline. Scientists design these compounds in the lab to block specific cellular growth and survival pathways affecting tumor cell function.

Avastin (bevacizumab), an antiangiogenic agent already approved to treat lung and colorectal cancers, shuts down the blood supply a tumor needs to grow and survive by binding to vascular endothelial growth factor (VEGF) molecules. Three phase II studies have shown Avastin has some activity in ovarian cancer. An ongoing phase III study adds Avastin to Taxol/carboplatin to see if Avastin makes the standard therapy more effective.

“Its level of efficacy seems to be similar to Doxil, topotecan, and the taxanes,” Dr. Thigpen says. For ovarian cancer, Avastin produced an overall response rate of 16 to 21 percent. Side effects experienced by clinical trial participants included bowel perforation, wound healing issues, and chest pain.

In another strategy, scientists created a decoy receptor called VEGF Trap (aflibercept). The VEGF molecules bind to the trap instead of helping the tumor grow new blood vessels. Preliminary results of a phase II study of 162 patients with recurrent platinum-resistant or refractory epithelial ovarian cancer were presented this past June at the annual meeting of the American Society of Clinical Oncology. Thirteen patients, or 8 percent, taking aflibercept had a partial response (measured as tumor shrinkage of at least 30 percent), and 41 percent of patients had durable stable disease after 14 weeks.

Other types of targeted therapy interfere with growth factors that cause tumors to grow. A majority of ovarian cancers express human epidermal growth factor receptors 1 and 2 (HER1 and HER2). Certain targeted therapies, like Herceptin (trastuzumab), can block the signals tumors use to stimulate growth. While helpful for breast cancer, preliminary research shows Herceptin is only minimally effective for ovarian cancer, Dr. Coleman says.

Pertuzumab, another compound that binds HER, may be more effective than Herceptin. The epidermal growth factor activates when two members of its family dimerize, or come together as a pair. Pertuzumab was designed to bind to the HER2 dimerization site, blocking this process. A phase II study showed a 14.5 percent clinical benefit (includes partial response and stable disease) in patients treated with the experimental agent. It was well tolerated, although it did cause diarrhea for most patients.

In the more experimental realm, scientists continue to look for new pathways a tumor might take in its quest to grow larger and stronger. DNA tests can show which drugs would be most effective against a patient’s unique type of tumor.

Since the protein Src is overexpressed in late-stage ovarian tumors, inhibiting Src may benefit patients whose tumors have become resistant to traditional chemotherapy. Two ovarian cancer trials at Duke University, set to open next year, will test a drug already approved for chronic myeloid leukemia, Sprycel (dasatinib), which blocks the Src pathway and therefore affects tumor growth factors.

Meanwhile, nearing approval is Yondelis (trabectedin), a drug derived from a sea squirt that appears to have anti-tumor activity in ovarian cancer by interfering with DNA replication. Initial European studies found 43 percent of advanced ovarian cancer patients responded to Yondelis with few side effects, though some patients experienced neutropenia and weakness when it was given following platinum- and taxane-based chemotherapy.

Despite these promising targeted therapies, Dr. Coleman says chemotherapy will remain important in ovarian cancer treatment because targeted agents work best in combination with chemotherapy. “These targeted therapies should really be looked at as part of a strategy,” Dr. Coleman says. “Our challenge is to determine which drug goes with which patient and which cocktail would be appropriate.”

While it’s exciting to consider the new treatments, physicians and their patients still struggle with a marked lack of early detection methods, though promising research in proteomics is gaining attention. Without good tests, ovarian cancer survival rates aren’t going to improve a great deal, Dr. Goff says. Until better tools come along, she says, the focus has to come back to the basics: good communication between doctor and patient.

“Although we do need an adequate screening test, I think we are years, if not decades, away from having that test,” Dr. Goff says. “But there is a possibility of making the diagnosis earlier by having women identify these symptoms and having doctors take these symptoms seriously.”