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SPECIAL ISSUE: WOMEN'S HEALTH

IN THE LAB

Stalking an insidious killer

Ovarian cancer is rare and often overlooked. Scientists hope protein markers can help them catch it earlier.

By ANDREAS VON BUBNOFF
Special to The Times

A few weeks ago, Lois Myers, 51, of Morristown, N.J., got rid of her wig. She had just ended a one-year-long chemotherapy regimen to treat a recurrence of ovarian cancer that had spread to other parts of her body.

In 1998, she'd been diagnosed with late stage ovarian cancer. She had her ovaries and uterus removed, but it was too late. The cancer had already spread.

The American Cancer Society estimates that this year about 20,000 women will be diagnosed with ovarian cancer. Of those, 75% will be diagnosed in an advanced stage of the disease, says Dr. David Fishman, director of the National Ovarian Cancer Early Detection program at New York University.

"Most of them will require horrible operations and chemotherapy and won't be alive five years later," Fishman says.

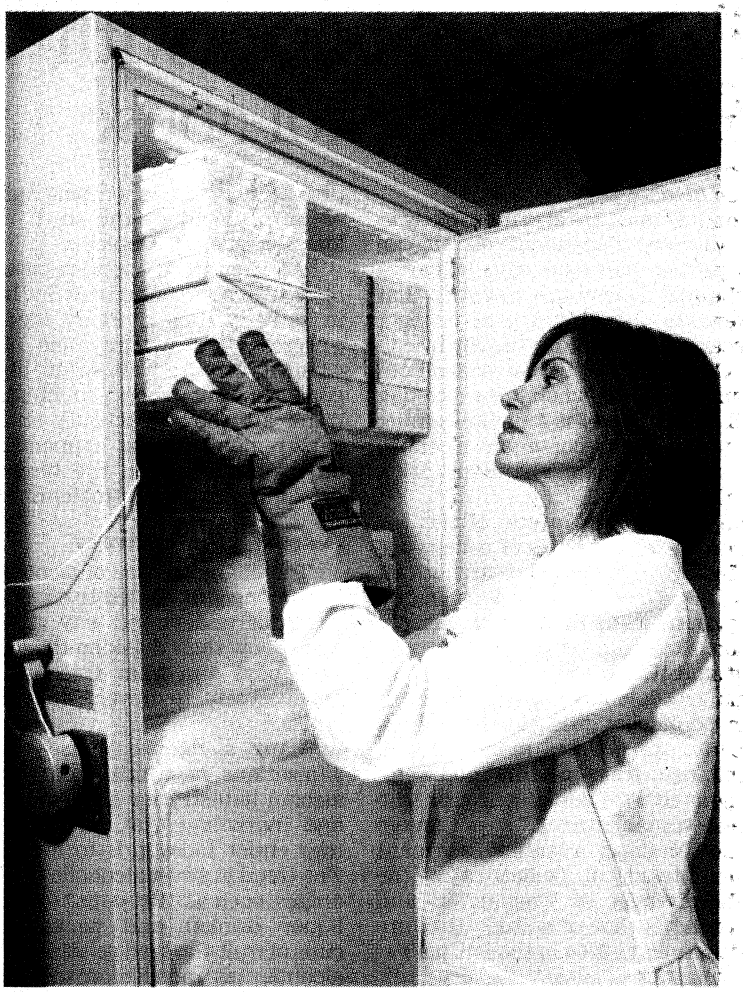
The key, experts say, is to detect the cancer early enough — before it spreads. But that's not easy because ovarian cancer is rare and often doesn't show obvious symptoms. Current ways to detect it often miss it at its early stages or wrongly identify cancer in healthy patients, which leads to unnecessary surgeries.

New research is underway to come up with better tools to detect the cancer early. "We scientists are beating every bush" to find them, says Emanuel Petricoin, codirector of the Center for Applied Proteomics and Molecular Medicine at George Mason University in Manassas, Va. He and other researchers are screening the blood and urine of patients in the hope they'll find a protein, or more than one, that increases or decreases in quantity when ovarian cancers begin to grow and which could ultimately be the basis of an accurate early test.

The scientists say they have leads, but many caution that it will be years before a test makes its way to the clinic. For one thing, ovarian cancer is so rare that any screen would have to be extremely accurate to avoid targeting many women who don't have it and subjecting them to invasive and unnecessary follow-up tests.

Ovarian cancer is an especially difficult cancer to catch because symptoms are often so subtle — things such as bloating and constipation — that patients and doctors dismiss them. (Myers, for example, said she did have symptoms such as bloating but just didn't think much about them. "I just thought I was under stress from work or from life," she says.)

There is no reliable laboratory test for early detection either. "We really have no tools that reproducibly detect early stage ovarian cancer, no blood test, no imaging, no nothing," Fishman says.



KAREN TAPIA-ANDERSEN *Los Angeles Times*

LABELED: *Dr. Beth Karlan freezes tumor samples, which were used to find a marker called HE4 that may detect ovarian cancer.*

Typically, if doctors suspect a woman may have ovarian cancer, they perform a pelvic exam to try to feel for any irregularity. They also get an image of the ovaries, often with ultrasound, and check the level of a blood marker called CA 125, a protein that's often present at higher levels in patients with ovarian cancer.

But pelvic exams often don't catch ovarian cancer until it is too late, says Dr. Robert Wenham, a medical oncologist and physician scientist at the Moffitt Cancer Center in Tampa, Fla. And the CA 125 test only detects 50% to 60% of early cancer cases, says Dr. Robert Bast, vice president of translational research at the University of Texas M.D. Anderson Cancer Center in Houston, who co-discovered the marker more than 20 years ago.

Another problem with CA 125 and ultrasound is that they too often raise false alarms in healthy women. And once there is suspicion, doctors often surgi-

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Finding the mark

[*Cancer, from Page F6*]
cally remove part or all of the ovary, only to discover later that there was no cancer at all. "Often, you just can't tell by looking at the ovaries if there is a cancer," Wenham says.

A recent study, part of the National Cancer Institute's Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial, which included almost 29,000 women ages 55 to 74, found that such false positive tests led to about 28 surgeries for each true cancer case.

To find a better test, some scientists are comparing blood from ovarian cancer patients and blood from healthy women to see if a whole bank of different proteins can together diagnose ovarian cancer better than a change in one protein alone. At a scientific meeting last month in Washington, D.C., Anna Lokshin, an assistant professor of medicine at the University of Pittsburgh, showed that changes in the blood levels of about two dozen protein markers correctly identified 90% of early cancer cases, while falsely identifying only 2% of women who didn't have cancer.

Other scientists are trying to find new markers.

One approach is to use microarrays, tiny chips that examine thousands of genes at a time to see which ones are active in cancerous tissues and make proteins that seep into blood or urine, says Dr. Beth Karlan, director of the Women's Cancer Research Institute and the Division of Gynecologic Oncology who studies such markers at Cedars-Sinai Medical Center.

In 1999, Karlan was part of a team that identified a new marker called HE4. In a preliminary study with a few dozen patients, HE4 was shown to detect as many cancer cases as CA 125 while identifying fewer false positives. Today, Karlan says, "We have thousands of markers coming into the pipeline."

Another approach to finding markers specific to ovarian cancer involves a method called mass spectrometry, which separates the thousands of proteins found in blood based on their different sizes and charges. Last year, Petricoin of George Mason University used the method to isolate and sequence 700 new markers specific to ovarian cancer. Studies are underway to test the markers' accuracy.

Although there are thousands of candidate markers, preliminary studies have so far only evaluated dozens of women with and without ovarian cancer in experiments that test blood or urine samples. These studies, researchers say, are still too small to know whether the markers could be used for large-scale population screening for early ovarian cancer.

There are several challenges.

One problem lies with the fact that ovarian cancer is so rare. Each year one in 2,500 postmenopausal women — the group primarily affected — develops ovarian cancer. This means that markers have to be near-perfect. Even a marker that falsely identified cancer in just 1% of healthy women could lead to 25 unnecessary surgeries a year for every real cancer case detected, Petricoin says.

What's more, the markers scientists have detected might be present in many types of cancers, not just ovarian cancer, making them less specific and accurate.

And the studies only use blood from women who had already been diagnosed with ovarian cancer. It's not yet clear whether the methods could detect the cancer earlier than the current methods.

In one effort to solve these problems, Lokshin and other researchers are collaborating to find an optimal set of markers. They'll test them on blood samples of ordinary citizens collected by the National Cancer Institute in its PLCO trial.

That trial has been collecting annual blood samples from almost 40,000 women for five years, before any of them were diagnosed with cancer. It will compare the blood in women who went on to develop ovarian cancer with those who did not. National Cancer Institute scientist Sudhir Srivastava, who directs the collaboration, says he is optimistic that in five years the effort will come up with a few effective biomarkers that can detect this difficult cancer early.

Myers has cofounded a foundation to raise money for ovarian cancer research: So far, she says, the foundation has given away about $700,000.

She is keeping her fingers crossed that her own cancer won't recur any time soon. "I was in a long remission — for seven years," she says. "I hope it will happen again this time."

Understanding your risk

Without a good ovarian cancer test, it's important to watch for symptoms such as bloating, constipation, pelvic pain, increased abdominal girth or urination.

The general population has a 1% to 2% chance of getting ovarian cancer in their lifetime, but those with a mutation in the BRCA 1 or BRCA 2 genes have a 40% and 20% risk, respectively, says Dr. Robert Wenham, a gynecological oncologist at the Moffitt Cancer Center in Tampa, Fla.

These mutations are more common in certain groups such as women of Ashkenazi Jewish ancestry. Women with a family history of early ovarian, breast, colon or uterine cancer are also more likely to get the cancer and should ask their doctor about genetic counseling.

Studies have shown that women who took contraceptive pills for 10 years reduced their risk by 70%, Wenham says. High-risk women who are finished having children should consider having their ovaries removed, he adds, which reduces the risk by 95%.