



# Hide and Seek

## WCP focuses new research on elusive ovarian cancer

Through the years, the cancer battle has witnessed hard-won gains and occasional dramatic turnabouts, as in childhood leukemia – once usually lethal, now mostly curable. While the road ahead is long, researchers are optimistic that many cancers will be tamed through prevention, improved detection, and combinations of new drugs aimed at tumors with pinpoint accuracy.

There's an urgent need for progress in ovarian cancer, one of the stealthiest of malignancies, which is difficult to detect in early stages and hard to defeat once it has spread. Researchers don't see any magic bullet on the horizon, but, says Ursula Matulonis, MD, of the Women's Cancers Program (WCP) at Dana-Farber, "I think this is a curable cancer; eventually we will do a much better job."

WCP researchers are attacking ovarian cancer on many fronts. New gene and protein technologies are being used to develop accurate early diagnostic tests. Scientists are tracing the faulty "wiring" that turns ovarian cells cancerous and are seeking better ways of detecting changes that lead to cancer. They're testing new treatments such as therapeutic vaccines, and

*Infusion nurse Cheryl Manzi, RN, BSN, (right) has been at Clare Matthews' side through all her chemotherapy treatments, creating a comforting bond.*

they're attempting to expand what's known about reducing ovarian cancer risk.

"The mission is to address the full range of detection, prevention, and treatment of ovarian cancer," says Daniel Cramer, MD, a gynecologist at DFCI and researcher at the Dana-Farber/Brigham and Women's Cancer Center.

Dr. Cramer is the principal investigator on a new federal grant, known as a SPORE (Specialized Program of Research Excellence), awarded in July to the Dana-Farber/Harvard Cancer Center to support collaborative research aimed at improving the outlook for ovarian cancer patients. DF/HCC – one of five ovarian cancer SPORE recipients in the nation – will receive \$11 million over the next four-and-a-half years to finance the projects.

Though ovarian cancer is significantly less common than breast cancer – 25,580 cases expected in 2004 vs. 215,990 cases – it is more lethal. The American Cancer Society expects 16,090 deaths in 2004, compared with 39,800 from breast cancer.

A woman's lifetime danger of ovarian cancer is 1 in 70, much less than her one-in-eight risk for breast cancer, and most of the risk comes at later ages – half of all women diagnosed are over 65 – though it can strike as young as the 20s.

The one glaring statistic that scientists are determined to raise is 37 percent – the five-year survival rate for all stages of ovarian cancer. Since five-year survival is 90 percent when the tumor is confined to the ovary, better detection would improve the overall cure rate.

Statistics tell one kind of story, but the challenges facing an individual patient with ovarian cancer give a more vivid tale. The journey of Clare Matthews over the past several years illustrates a typical experience and the strategies that WCP researchers are deploying to fight the formidable disease.

## Puzzling symptoms

Matthews, 58, sits at her dining room table over coffee, emanating a deeply positive attitude that's quietly spoken, not greeting-card flowery. When she says, "I am blessed" – and she says it frequently – it's clear she means it. Recently, she recounted the delayed diagnosis of her ovarian cancer, her subsequent treatment with surgery and chemotherapy, and two recurrences of the disease.

In the spring of 2001, Matthews noticed on-and-off abdominal pain and pressure in her rectum. The symptoms did not alarm her or prompt her doctor to suspect an unlikely cancer. An intestinal specialist didn't find anything amiss and suggested she might have a benign cyst in an ovary. Since she had no pain when she saw him, he didn't suggest taking the matter further unless the pain returned.

This scenario is the hallmark of early ovarian cancer: no symptoms, or ones that come and go or are associated with much more common conditions that aren't dangerous, like indigestion or irritable bowel syndrome.

"This is very typical," notes Dr. Matulonis, Matthews' medical oncologist. "A woman notices abdominal fullness or bloating, constipation, pain, and other symptoms caused by the pressure of the growing tumor, yet the exam may be benign until the cancer is advanced." In fact, 70 percent of ovarian cancers are in advanced stages when diagnosed.

By late summer, Matthews' discomfort returned. This time, her primary care doctor noticed fullness in her pelvis, ordered an ultrasound, followed by a CT scan, and referred her to a gynecologic oncologist. Some five months after her first symptoms, the picture snapped into focus. "We're talking definite malignancy here," the specialist told her. The tumor had spread to the lining of her abdomen, putting her in the third of four stages of the cancer's progression.

## Symptoms of ovarian cancer

These are some of the potential signs and symptoms of ovarian cancer:

- Unexplained change in bowel and/or bladder habits such as constipation, urinary frequency, and/or incontinence
- Gastrointestinal upset such as gas, indigestion, and/or nausea
- Unexplained weight loss or weight gain
- Pelvic and/or abdominal pain or discomfort
- Pelvic and/or abdominal bloating or swelling
- A constant feeling of fullness
- Fatigue
- Abnormal or postmenopausal bleeding
- Pain during intercourse

*(Source: National Ovarian Cancer Coalition)*

## Stages of ovarian cancer

### Stage I

Cancer is confined to one or both ovaries.

### Stage II

Cancer is found in one or both ovaries and/or has spread to the uterus and/or fallopian tubes and/or other tissues within the pelvis.

### Stage III

Cancer is found in one or both ovaries and has spread to lymph nodes or to other tissues inside the abdomen, such as the surface of the liver or intestine.

### Stage IV

Cancer has spread outside the abdomen or has spread to the inside of the liver.

(Source:  
*National Cancer Institute*)

## Early warning needed

Matthews' case highlights the need for a true early-detection test. It would be a huge lifesaver, but developing one has been enormously difficult. The current gold standard, sensitive ultrasound imaging using a probe inserted into the vagina, is too costly to use in screening, and it can miss the early stages of a cancer if it's not in the form of a lump.

Rising levels of CA 125, a blood protein, can be a signal of ovarian cancer, but the test is not reliable enough for screening. The best hope for early detection, believe Dr. Cramer and colleague Samuel Mok, PhD, may be blood tests that spot abnormal proteins secreted into the bloodstream by tumor cells as the disease develops. (The hunt for telltale patterns of proteins, called "biomarkers," is detailed in the 2004 Winter/Spring issue of *Turning Point*, p. 12.)

As part of the SPORE, Dr. Mok is also examining stored tissue samples from ovarian tumors in search of the earliest abnormal changes to guide research on detection. Judy Garber, MD, MPH, director of the Friends of Dana-Farber Cancer Risk and Prevention Clinic, and Steven Skates, PhD, a biostatistician at Massachusetts General Hospital, will be comparing blood specimens taken before and after surgery from high-risk patients who had their ovaries removed to prevent cancer.

Working similar territory is Ronny Drapkin, MD, PhD, of Dana-Farber's Cancer Biology Department, who rounded up the most common ovarian cancer-related protein patterns described in several different studies. From this small collection, Dr. Drapkin identified a protein, HE4, as a promising biomarker for ovarian cancer. He says that HE4 might be useful as a screening test, and – because cancer cells with less HE4 don't grow as well – might even be attacked with targeted drugs as a form of treatment.

## The cancer spreads

Clare Matthews' diagnosis prompted an appointment with Ross Berkowitz, MD, director of Gynecologic Oncology Services at the Dana-Farber/Brigham and Women's Cancer Center, who would perform her surgery. "The shock had hit me, and Dr. Berkowitz was incredible: He was so calming," she recalls. "He didn't sugarcoat the situation, but asked questions. He spent well over an hour with me, and I had a date for surgery before I walked out of the office."

Dr. Berkowitz performed the usual oophorectomy (removal of ovaries and tubes) and hysterectomy (removal of the uterus) for ovarian cancer and succeeded in removing the solid tumor. However, he also found small tumors on her omentum (a layer of tissue that covers the stomach and intestines), and fluid washed from her abdomen revealed rogue cancer cells outside the ovaries. Because her cancer was in Stage III, she would need chemotherapy to thwart a recurrence.

One of the standard chemotherapy regimens for ovarian cancer is a combination of carboplatin and taxol, which makes some women miserable while others have less severe side effects. Matthews underwent six rounds of chemo – once every three weeks – in the fall and winter of 2002. Antinausea agents kept her feeling well enough to continue working with her partner in an environmental consulting business that requires travel. She also enrolled in a mind-body stress reduction study for ovarian cancer patients, which she found "wonderful."

After treatment, Matthews returned to DFCI every three months for imaging scans and measurements of CA 125, which can signal a recurrence of cancer if it climbs after treatment. After five months, Matthews' CA 125 blood levels did rise, and a CT scan detected a regrowth of her cancer. Repeated chemotherapy succeeded in beating the cancer back, but five months after the treatment ended, Matthews had another recurrence. Again she underwent chemotherapy, finishing in January 2004.

## Better therapies needed

While ovarian cancer can't yet be prevented, its risk can be reduced. Taking oral contraceptives for at least five years cuts the danger in half for some types of the disease. Tubal ligation also reduces risk, and diets high in lycopene (a component of tomato sauce) and the antioxidant carotene (found in yellow-orange fruits and vegetables) have been found to be protective.

Dr. Berkowitz says, "The greatest opportunity to have a dramatic impact on improving survival in ovarian cancer is by advancing our capacity to improve prevention as well as early detection." Still, Dr. Matulonis says, until more powerful preventives are identified and effective early-detection tests become available, "there is a need to continue developing better therapies once the disease is diagnosed."

Plaguing the treatment of this cancer is the tendency of ovarian tumor cells to become resistant to drugs that initially halted the disease. In one of the SPORE projects, Alan D'Andrea, MD, of DFCI, and Michael Seiden, MD, a medical oncologist at Massachusetts General Hospital, will use a new test to determine when ovarian tumor cells become resistant to platinum, one of the standard chemotherapy agents. The sooner they can find out, the sooner doctors can switch to other, usually experimental, drugs that may fight the tumor better. They're also testing compounds that might be able to make a resistant tumor susceptible again.

Individualized vaccines are another new weapon in the attack on ovarian cancer. These therapeutic vaccines, made from a patient's own tumor cells and modified with genes, have had some success in other forms of cancer, stimulating the immune system to stiffen its defenses against tumor cells.

Marcus Butler, MD, of the WCP and his colleagues have tested such a vaccine in Phase I trials in women with advanced ovarian cancer. Researchers implanted immune-stimulating genes into tumor cells so that, when the vaccine was injected into patients, their immune defenses would readily recognize and attack the remaining ovarian disease.

"We're seeing signs of immune responses in the skin," says Dr. Butler, but whether the defensive cells are fighting the residual tumor cells isn't yet clear. Two additional trials will open in late 2004 or early 2005, he says, to find out if the vaccine can reduce the chances of recurrence in women who are currently in remission.

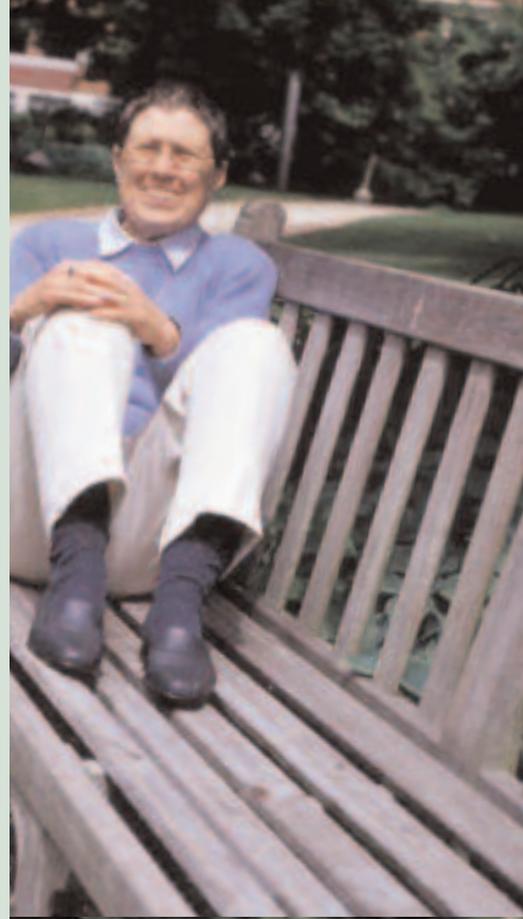
SPORE funding will enable Donald Kufe, MD, of Dana-Farber, to test a vaccine that targets a protein, MUC-1, that is overproduced in some kinds of cancer, including ovarian. He said the first human tests could begin this year.

## Waiting and watching

As rapidly as researchers are pressing forward, ovarian cancer patients today live with much uncertainty. The disease challenges them to focus on the present and remain hopeful, even though the odds may be daunting. There's no better role model than Clare Matthews. "I'm forging ahead with life," she says. "I have come to look at my ovarian cancer as a chronic illness that recurs periodically and then is beaten back."

"We're catching the recurrences early, and as long as there are treatments, I can live with this," she declares. "Fortunately, the Women's Cancers Program has an array of clinical trials that offer other options should the standard treatments fail."

Matthews adds that Dana-Farber means much more to her than a center of medical excellence. "I have had the same nurse, Cherilyn Manzi, RN, BSN, for all my infusions, and that consistency – as well as that of my doctors, Dr. Matulonis and Dr. Berkowitz – makes all the difference. We've developed a rapport, and approach my cancer as a team." And, even though returning to DFCI to be checked for recurrences causes her some anxiety, she says, "Dana-Farber is an unbelievably calming place for me." **RS**



*After ovarian cancer treatment and two relapses, Clare Matthews prizes each day and calls herself "blessed."*