A DIFFERENT APPROACH TO CANCER RESEARCH

Today in the United States, one woman will be diagnosed with a gynecologic cancer every seven minutes. Dr. Beth Karlan and her team of experts at the Women's Cancer Research Institute are fighting an important battle to educate, understand, and, ultimately, end the threat of gynecologic cancers to women.

BY VANESSA MCGRADY

Dr. Beth Karlan's interest in medicine began when she was a small child, with her favorite TV show, *Dr. Kildare*. "When I fantasized about my role on the show, I always saw myself as a doctor on the team," she says with a smile.

It seems that nothing could divert her from this path. Not the pediatrician who told her she could not be a doctor because she would "take a job away from a man." Not her mother, who, upon learning that her daughter had been accepted to Harvard Medical School, said "I sent you there to marry a doctor, not be a doctor." (Her mother quickly came around to becoming one of her biggest supporters. And Beth did end up marrying a surgeon—Scott Karlan.)

Her steely resolve has helped Dr. Karlan become one of the world's foremost experts on gynecologic cancers. The holder of the Board of Governors Chair in Gynecologic Oncology, she sees an average of 30 patients a week and helms several projects crucial to better cancer detection and treatment, including directing the Division of Gynecologic Oncology in the Department of Obstetrics and Gynecology, the Women's Cancer Research Institute, and the Gilda Radner Cancer Detection Program at the Samuel Oschin Comprehensive Cancer Institute.

With her team of researchers, Dr. Karlan is exploring innovative, more personalized approaches to cancer treatment. "The traditional 'slash, burn, and poison' approach (surgery, radiation, and chemo) is being replaced by individual targeted treatments," says Karlan. "Our goal is to find a way to minimize side effects and invasive procedures by targeting specific errors in a cell—errors that make it a cancer cell—and to destroy it while sparing the

Beth Karlan, M.D. pulls samples from the Women's Cancer Research Institute Tissue Bank (see page 15).

Ilana Cass, M.D. confers with her colleague, Andrew Li, M.D.

Quality translational research—work that quickly translates basic research findings into real medical treatments for patients in need—is the cornerstone of the Women's Cancer Research Institute.

normal tissues around it."

Besides her husband and children, Dr. Karlan says she is most proud of the multi-disciplinary team she has built at Cedars-Sinai. "I put together a team of committed researchers who are truly devoted to ending cancer as a threat to women," she says. Their quality translational research—work that quickly translates basic research findings into real medical treatments for patients in need—is the cornerstone of the Women's Cancer Research Institute.

One of these committed physicians is Dr. Ilana Cass. She jumped at the chance to work with Dr. Karlan in the summer of 1998, moving to Los Angeles from the East Coast after she finished her training. "It was a leap of faith. I had heard wonderful stories about Beth's commitment to research and to patient care. She was able to successfully do both, and she was considered one of the most important role models for women in our field," Dr. Cass says. "I thought, 'I trust this woman; she is going to take care of me.'"

Dr. Cass expanded Dr. Karlan's original work in characterizing abnormal genes that occur in cancers in the female reproductive tissues, including the ovaries, fallopian tubes and the peritoneum—the thin, transparent membrane that lines the abdomen and covers certain organs. *Continued on page 12*

The Sargents' Race for *Her*

FOR A YEAR AND A HALF, NANCI SARGENT HAD symptoms of ovarian cancer—bleeding, bloating, and lower-back pain —and disregarded them. "The thought of a second cancer never entered my mind," says Nanci, who had overcome Hodgkins lymphoma 14 years earlier.

In May 2000, Nanci was diagnosed with stage 3 ovarian cancer. With the help of her children, Nicole, Scott, and Kelli, and husband, Mike, she is now courageously fighting her second battle with cancer.

The Sargents are also determined to fight for other women like Nanci by raising awareness about ovarian cancer through RUN FOR HER.

RUN FOR HER is the brainchild of daughter Kelli, who conceptualized the 5k/3k run as part of her master's thesis in the Sports Management Program at the University of San Francisco and organized it with the help of Cedars-Sinai Medical Center. Nanci's husband, Mike, a retired stockbroker, has joined in the effort: He spends his time on the computer, answers phones, rallies sponsors—he does whatever is needed.

Last November's inaugural race with 1,000 participants raised more than $225,000 to benefit the Women's Cancer Research Institute at Cedars-Sinai. Most of that support, Mike says, was from individual donors and the Sargents' grassroots efforts.

It is Nanci's dearest hope that the money raised will help Dr. Karlan and the research team at Women's Cancer Research Institute develop a test to detect ovarian cancer in its early stages. There is currently no reliable method of early detection for ovarian cancer.

Through outreach and education, the Sargents want to make sure men and women from every walk of life know about the symptoms of ovarian cancer, the deadliest of all gynecologic cancers. "Men have to be receptive as well," Mike says. "Maybe I should have been more aware [of the symptoms] too."

Nanci seconds her husband: "It was my lack of awareness about the symptoms of ovarian cancer that kept me from seeking the help of my doctors. I am thankful every day for the amazing expertise, compassion, and devoted care provided by Dr. Beth Karlan and her colleagues," she adds.

The Sargent family at last year's Run for Her (L to R): Nicole, Mike, Nanci, Kelli, and Scott

Nanci has found the silver lining in this experience: unbridled love from friends, family, and strangers. Every day, people approach Nanci with a hug and offer their own stories. "There's been amazing, flourishing support. If you could bottle that, it would put a smile on your face every day," Nanci says. "I receive every ounce of it."

FINDING THE MARK

Every hour, nine women in the United States are diagnosed with a form of gynecologic cancer. While new treatments and cures are rapidly developing, the key is to detect the cancer early enough—before it spreads. The Ovarian Cancer Biomarker Discovery Project does just that.

Established in partnership with the L & S Milken Foundation, this initiative searches for a molecular "signature" for ovarian cancer. A biomarker is a biochemical feature that can be used to measure the progress of disease or the effects of treatment.

"Early detection is most important. Discovering these biomarkers is useful because most ovarian cancers are only detected very late, in stage 3 or 4," Dr. Karlan says, adding that those cancers caught in stage 1 are 90 percent treatable because they are confined to the ovary. In stages 3 and 4, the tumor has spread around the abdominal cavity or even farther throughout the body. "The hope for a five-year survival at that point is only 15 to 35 percent," Dr. Karlan says.

The project will likely have applications for other kinds of cancers in different populations. For example, her colleague Dr. Andrew Li is working with genetic alterations in androgen receptors, which could help researchers gain insights into prostate cancers.

"We are discovering that androgens, or typical 'male' hormones, play an important role in ovarian cancer," says Dr. Li. "Our work has already demonstrated that patients whose tumors have a very active androgen receptor have a worse prognosis. We are beginning a clinical trial that looks at blocking that receptor."

Dr. Karlan's team is also focusing on gene mutations called BRCA1 and BRCA2, which are more common in certain groups, such as women of Ashkenazi Jewish ancestry. The general population has a 1 percent to 2 percent chance of getting ovarian cancer in their lifetime, but those with a mutation in the BRCA1 and BRCA2 genes have a 40 percent and 20 percent risk, respectively.

It is Dr. Karlan's hope that her work with these genes will help find a method for detecting gynecologic and other cancers in different populations. The study, she says, might not give us all the answers but may clear a pathway for doctors to get closer to a positive outcome.

Andrew Li, M.D. and research associate Klara Armstrong look at "western blots" in order to understand the molecular mechanisms behind ovarian cancer survival rates and short androgen receptors.

Despite the many challenges Dr. Karlan and her team face in their exploration of new treatments and cures for ovarian cancer, she sees a bright future, with more effective, targeted therapies a mere five years away. "We are starting to better understand the 'cogs and wheels' that make a cell cancerous. We are also much more intelligent and discreet about how we design trials, drugs, and new therapies to treat cancer effectively, with fewer side effects."

Inroads into early detection are also being made for breast cancer. Because 85 percent of breast cancers begin in the ducts (the milk passages), Dr. Karlan and her team are leaders in a national study to remove fluid from breast ducts to detect abnormal cells using ductal lavage, a process similar to a Pap smear. While Karlan does not foresee the ductal lavage as part of a routine check for every woman at her annual gynecological exam, she does hope it becomes a standard for women with high risk factors. It would make it possible to learn about potential problems early on, or to take appropriate action while the cancer is in its most curable stage.

"Using the ductal lavage fluid to discover potential biomarkers may lead to a blood test that could aid imaging (such as mammography) in diagnosing breast cancers before they develop," Karlan says.

Beth Karlan is lucky enough to occasionally work with her husband, Dr. Scott Karlan, director of Physician Education at the Saul and Joyce Brandman Breast Center at Cedars-Sinai, a project of the Women's Guild. Sometimes they operate together. They collaborated on the ductal lavage project, and Scott Karlan brought in the breast cancer component for the tissue bank.

Dr. Beth Karlan admits that professionally, she gets the most satisfaction from caring for her patients. She spends half her time researching ways to give them more time and a better quality of life. "The physician-patient relationship is a sacred bond," she says. "Cancer is so complex. Each cancer is a different disease, each person is really quite unique."

BANKING ON A CURE FOR CANCER

In 1990, Dr. Beth Karlan spearheaded the development of a gynecologic cancer tissue bank. Today, the Women's Cancer Research Institute's Tissue Bank holds more than 2,800 samples from patients all over the country. It is one of the world's most comprehensive gynecologic inventories of cancerous and noncancerous tissue, allowing the WCRI and affiliated scientists to study cancer at every stage of its development.

The goal is for the different samples of breast, ovarian, cervical, uterine, and fallopian tube tissue—along with blood, ascites (abnormal buildup of fluid in the abdominal cavity), nipple aspirate, and urine—to help researchers understand the contributing genetic causes of cancer.

In addition, the bank seeks to identify why some tumors seem impossible to control, and how to find new ways to beat them. "Women die because tumors develop resistance," Dr. Karlan says. "We are using the tissue bank to do genetic analysis to identify the root causes of resistance and target those in therapy."