LEADING THE CHARGE AGAINST

Ovarian Cancer

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photo: Stu Rosner
IT TAKES ALL KINDS

The robust collaborative environment at BWH brings together all kinds of specialists to tackle ovarian cancer. Pictured from left to right are epidemiologist Susan Hankinson, RN, ScD; surgeon and program director Ross Berkowitz, MD; surgeon Michael Muto, MD; epidemiologist Daniel Cramer, MD, ScD; and pathologist Christopher Crum, MD.
Early in his medical career, Michael Muto, MD, had a haunting revelation. It was the 1980s, and he kept meeting members of the same New England family. The women, both mothers and daughters, were coming to Brigham and Women’s Hospital (BWH) in various stages of ovarian and breast cancer. Physicians and researchers at the time knew there was a connection in cases like these, but didn’t yet know what it was. A decade later, it would be revealed that mutations in certain genes called BRCA1 and BRCA2 were handed down to each next generation, greatly increasing the chance of getting cancer.

Ovarian cancer is often undetectable until the disease is past the stage when surgery and other therapies can eliminate it. Muto vividly remembers the family because of the unusual cluster of ovarian and breast cancers—and because of the terrible tragedy the cancers wreaked on the family members. “I never wanted to see another family go through this hideous, awful situation again,” he recounts. “I and my colleagues were adamant that there must be something we could identify and treat to stop this from happening.”

Muto and Daniel Cramer, MD, ScD, director of BWH’s OB/GYN Epidemiology Center, created what’s now called the Cancer Risk and Prevention Center, a joint effort of BWH and the Dana-Farber Cancer Institute. At the center, they documented patients’ histories of ovarian cancer, performed ultrasounds, offered preventive surgery for those at high risk, and conducted blood testing for the biomarker CA125. Like prostate-specific antigen (PSA) is a biomarker for prostate cancer, the biomarker CA125 is elevated in the blood of women who are diagnosed with ovarian cancer. The problem is, the substance doesn’t rise until the later stages of ovarian cancer—and the challenge with ovarian cancer is that it is generally only diagnosed in late stages, which makes it difficult to catch and cure.

“Clearly, we’d like to find a marker that is actually elevated a year or two years prior to diagnosis,” says Cramer.

With the combined efforts of Brigham and Women’s physicians and scientists, this goal is closer than ever. “We have an incredible resource in that we have the largest and most advanced gynecologic pathology department in the world,” says Ross Berkowitz, MD, director of Gynecology and Gynecologic Oncology at BWH. He points out that the robust collaboration among pathologists, molecular biologists, epidemiologists, surgeons, and even patients has positioned the hospital to recognize the disease in the early stages, before it spreads—or to reduce the factors that lead to its occurrence in the first place.

REDUCING CANCER RISK

As an epidemiologist, Cramer has been studying large groups of women for years to determine why some get ovarian cancer while most stay cancer-free. So has Susan Hankinson, RN, ScD, principal investigator of the Nurses’ Health Study, the groundbreaking large-scale study of more than 120,000 nurses that began at BWH in 1976 and continues to this day.

Using Nurses’ Health Study data, BWH researchers have uncovered many intriguing connections over the years. When studies started showing that women who take oral contraceptives have a reduced risk of ovarian cancer, Hankinson and her colleagues went further.
“What we asked is, ‘How long does that reduce risk?’” she recalls. “It looks like the protection lasts for at least 20 years, but after that it starts to subside.”

Now Nurses’ Health Study researchers are examining whether women who work the night shift might be at increased risk for ovarian cancer. “Melatonin appears to protect against cancer, but people who have their circadian rhythms altered by working at night and sleeping during the day can have suppressed melatonin levels,” Hankinson says. “Our research group will be the first to assess these exposures with ovarian cancer.”

Cramer made the observation years ago that women who use talcum powder in their hygiene regimen might be at greater risk for ovarian cancer. Studies over the years have proven him right: They show an association between talcum powder use and incidence of the cancer. “Our studies suggest that the talc causes inflammation in the lower genital tract and migrates to pelvic lymph nodes, leading to immune disregulation,” he explains.

PROTECTIVE MEASURES
Other risk factors Cramer analyzes deal with chronic inflammation and lowered immunity. For instance, having a baby, breastfeeding, or taking oral contraceptives are all positive forces against ovarian cancer, lowering a woman’s risk. Those actions are similar in that they all curb ovulation. “That led to the theory that it’s repeated ovulation that’s causing the problem,” Cramer says. Conversely, women who have never had a baby are at increased risk.

But there is more to it than that, as Cramer’s research reveals. Why are women who have the mumps—i.e., inflamed salivary glands—during childhood at decreased risk? Also at lower risk are women who had an infection called mastitis while breast feeding, as well as those who had their “tubes tied,” i.e., tubal ligation. The key, says Cramer, is that these events involve tissues that all express a protein called human Mucin 1, or MUC1, which is a protein that is also found in ovarian cancer cells.

Cramer proposes a compelling theory: that acute injury or inflammation of these tissues releases a tumor-like form of MUC1, which, in turn, causes anti-MUC1 antibodies to form, antibodies that could recognize and destroy early ovarian cancer. “Thus, the woman who is more likely to develop ovarian cancer has a relative absence of events like mumps in her younger life,” he explains. “Her immune system isn’t primed to recognize and eliminate ovarian cancer precursors.”

Cramer is collaborating with Hankinson to develop important data in support of this hypothesis. Someday he hopes to see a vaccine that will be able to build a shield of the protective antibodies or oppose the effects of the chronic events such as talcum powder use and repeated ovulation.

THE PATH TO PREVENTION
BWH pathologist Christopher Crum, MD, turned to ovarian cancer prevention after a productive career in the field of cervical cancer. He worked with a Nobel-winning group of physicians and researchers in the early 1980s to identify the critical link between precancerous changes in the cervix and human papilloma virus (HPV) type 16. These and other early studies supported the premise that HPV vaccines targeting precancerous changes would prevent cervical cancer. “The promise is real that the current vaccines can be improved to someday reduce cervical cancer by 70 to 80 percent,” Crum explains.
As with cervical cancer, Crum envisioned that ovarian cancer must have its own precancer: The trick was to find it. What he discovered was a real eye-opener in the ovarian cancer research community.

Crum started by looking for the origins of a highly malignant type of early cancer in women with inherited BRCA1 or BRCA2 gene mutations. He found that many of these “ovarian” cancers did not start in the ovary as previously thought—instead, they began in the distal fallopian tube. “Chris Crum developed a theory that the fimbriated end of the tube, the flower-like part, was actually where the cancer started in many BRCA patients,” Muto explains.

Though still controversial, the discovery has been monumentally important to ovarian cancer researchers, because they have a new target for tracking down precancerous changes. Instead of focusing strictly on the ovary—which gives rise to many tumors as well—they are now examining a precancerous pathway in the distal fallopian tube. Precancerous changes that they found in the tube proved that the cancer was originating in the tube, rather than spreading to it.

Searching deeper into the occurrence of cancer in the distal end of the tube brought additional revelations for Crum and his team. The precancer they found there contained a mutation in a gene called p53. In the future, physicians may be able to use this information about early changes in p53 or other genes in the tube to either prevent these changes from occurring or to identify women at risk for this disease, which would give doctors a powerful, new weapon in their cancer-fighting arsenal. “We know what the precancerous lesions look like, and we’re beginning to characterize them by determining the mechanisms that produce a true cancer,” says Crum.

**SEARCHING FOR A GOOD BIOMARKER**

Daniela Dinulescu, PhD, MS, describes herself as deeply committed to the early detection of ovarian cancer. For Dinulescu, it’s personal: Ovarian cancer took the life of a close friend of hers, despite the best care and treatment modern medicine could provide at the time.

Dinulescu’s idea is not only to uncover new biomarkers like CA125, but also to screen for those biomarkers differently. Instead of waiting until they accumulate in the blood—which, in CA125’s case, means that the ovarian cancer is already spreading throughout the body—she wants to use imaging technology to identify biomarkers in precancerous lesions or in early cancers that are limited to the ovary. Such a strategy would allow physicians to identify a potential dangerous lesion prior to malignancy or at the earliest stage of tumor development, when it is curable with surgery alone.

**TRACKING PRECANCERS**

The brown cells in this benign fallopian tube have the same mutations seen in ovarian cancer. Pathologists like Christopher Crum, MD, are studying these “precancers” to devise ways to interrupt the pathway to ovarian malignancy. “These cells have the features of cancer but are not yet malignant,” explains Crum.
Advances in mass spectrometry and medical imaging technologies are making it easier for physicians to detect disease in its earliest stages, supporting Dinulescu’s concept. “The theory is to inject a microscopic particle or antibody with a fluorescent label that would bind to and light up biomarkers on the surface of cancer cells within suspicious lesions,” she explains.

So far, she and her team have discovered some promising biomarkers. “If you add these markers to CA125, you can increase the sensitivity of identifying early-stage disease,” says Dinulescu. Catching early lesions before they have a chance to develop into ovarian cancer makes a world of difference in survival rates, which is her goal. “I didn’t go into this field wanting just to extend life, but to come up with a cure,” Dinulescu states. “At Brigham and Women’s, I get to work with great ovarian cancer clinicians and researchers to make a real impact in both cancer prevention and early diagnosis.”

THE IMMUNE RESPONSE

Like Dinulescu, Cramer also studies biomarkers: 27 different ones using specimens obtained prior to a diagnosis from the Prostate, Lung, and Colorectal Screening trial. Collaborating with investigators from other prestigious hospitals, such as the Hutchinson Cancer Center, the MD Anderson Hospital, and the Yale Medical Center, he conducts testing on different groups of biomarkers, looking for which ones showed up in the earliest stages of disease.

The disappointing conclusion was that CA125 remains the best single biomarker for ovarian cancer, with little value added by other markers. Unfortunately, all the markers tended to lose their signal for detecting ovarian cancer, even if the woman from whom they came was just a year from the cancer diagnosis, Cramer explains. But given the importance of the biomarker CA125, Cramer says more research is necessary. “Although CA125 has been around for 30 years, it was less than 10 years ago we learned it was in the same family as MUC1—and we still can’t explain why about 20 percent of women with advanced ovarian cancer have normal CA125 levels.”

The deeper Cramer went with this theory, the more interesting possibilities arose. “I realized there might be similarities between MUC1 and CA125—that tumor-like forms of CA125 might create anti-CA125 antibodies. These antibodies could actually bind to free CA125 and hide it,” he posits. Together with a colleague who is also interested in antibodies against tumor proteins, Cramer has developed a test to detect these immune complexes. The test may have value to both detect ovarian cancer at an early stage and to better follow ovarian cancer patients with normal CA125 levels.

PROTECTING THEIR PATIENTS

Together, physicians and researchers at BWH—like Muto, Cramer, Hankinson, Crum, and Dinulescu—are focusing on pre- and early malignancies in the fallopian tube. Understanding environmental effects, genetic factors, and the real impact of immune disorders should be a great boon to stopping the destruction of ovarian cancer.

Because of the hospital’s large genetic program and the number and rarity of the cases its physicians see, BWH is in a unique position to lead these breakthroughs. “Our robust clinical service means lots of patients to boost our understanding of ovarian cancer, so we can advance treatment,” explains Berkowitz.

It comes down to the mechanisms that force the disease to progress to true cancer, and whether changes on the molecular level can be halted—such as the effect of a genetic mutation—to prevent the cancer from happening at all. “We are optimistic about the ideas we’ve had for early detection,” says Cramer, “and I’m beginning to see some cracks in the shell of this disease, leading to our better understanding of it.” ♦

HOW YOU CAN HELP

If you’d like to support the efforts of BWH researchers and scientists as they search for early detection methods, identify biomarkers, and uncover risk factors of ovarian cancer, please contact Sue Andrews in the BWH Development Office at 617-424-4349 or sjandrews@partners.org.