Some of the operations performed by breast-cancer surgeon Shelley Hwang may no longer be needed if better biomarkers for breast cancer are found.

SHAWN ROCCO/DUKE MEDICINE

MOLECULAR BIOLOGY

Marked progress

Reliable markers could eliminate surgery and radiation therapy for many women diagnosed with a type of cancer that often does not progress beyond its non-invasive form.

BY HANNAH HOAG

Twelve years ago, Mary Jane Lapinski had a routine breast-cancer screening mammogram at her local hospital in Baltimore, Maryland. The mammogram showed multiple specks in her left breast. Her physician called it ductal carcinoma *in situ* (DCIS) — an early-stage, non-invasive cancer of the milk ducts. A surgeon told her he could attempt a lumpectomy to remove the lesions, but he recommended a mastectomy — removal of the entire breast. "I kept thinking, this isn't logical," says Lapinski, who was 48 at the time. "It was mind-boggling that a non-invasive cancer carried the same or more aggressive treatment than an invasive cancer."

The rogue cells in Lapinski's breast occupied a diagnostic grey area. Some cases of DCIS advance to invasive breast cancer, metastasis and death, but most do not. By current estimates, 20–30% of DCIS tumours will become aggressive within 20 years, says Shelley Hwang, a breast-cancer surgeon and researcher at Duke University School of Medicine in Durham, North Carolina. Still, most oncologists feel that it is best to remove the lesions and offer radiation treatment to stave off their progression.

The trouble is that oncologists cannot tell for certain which DCIS lesions will remain idle and which will turn deadly. Identifying breast-cancer biomarkers — molecules that can identify the pre-cancerous cells that are likely to progress to invasive cancer — could lead to better-informed decisions about treatment. Unfortunately, little is known about the natural history of DCIS. It is difficult to track the course of the disease because so many women undergo surgery. "If we can identify a subset of patients that are at risk of developing an invasive cancer and only treat those, we would spare many women unnecessary treatment," says Eileen Rakovitch, a radiation oncologist at Sunnybrook Health Sciences Center in Toronto, Canada.

SURGING DIAGNOSIS

Before the introduction of widespread screening mammography in the 1980s, DCIS lesions represented about 3% of breast cancers in the United States. They now account for nearly one-third of newly diagnosed breast cancers[1]. But detecting DCIS does not necessarily add much information about a woman's future or overall health. "It is entirely possible to find cancers that don't matter," says H. Gilbert Welch, an internist and cancer epidemiologist at the Geisel School of Medicine at Dartmouth in Hanover, New Hampshire. Welch and Archie Bleyer, then at the University of

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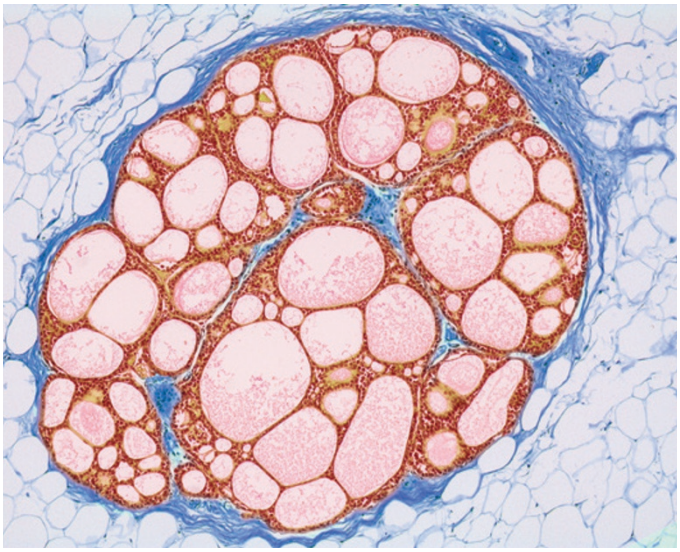
Texas Medical School in Houston, estimated that, in 2008, 70,000 US women received an early-stage breast-cancer diagnosis for lesions that would not have led to clinical symptoms, accounting for 31% of screening-detected breast cancers[2].

Most women diagnosed with DCIS have a lumpectomy or mastectomy — or a double mastectomy — along with radiation therapy. But the benefits of such treatments are hard to find. A much-discussed observational study of more than 100,000 US women with DCIS found that women who had lumpectomies or mastectomies to treat DCIS had just a 3.3% chance of dying of breast cancer in the next 20 years, not much different than the risk to women in the general population[3] (2.7%, according to the American Cancer Society).



STEVE GSCHMEISSNER/SPL

Ductal carcinoma *in situ* is a common type of non-invasive breast cancer.

Ideally, women with DCIS would be tested to assess whether surgery is the best course of action. Although no such test is clinically available, physicians are starting to use biomarkers to predict the future of women who have already had surgery. One test — Oncotype DX DCIS Score, produced by Genomic Health in Redwood City, California — stratifies women who have had breast-conserving surgery for DCIS into low, medium and high risk for future cancer. The test evaluates the expression of seven cancer genes (including those associated with cell proliferation and hormone receptors) in tissue samples taken from breast biopsies.

Rakovitch validated DCIS Score in a retrospective study of women diagnosed with DCIS and who'd had breast conserving surgery. In work funded by a research grant from Genomic Health, she and her colleagues applied the test to tissue samples from 718 women[4]. "Women with an intermediate- or high-risk score had twice the risk of developing local recurrence compared to women with a low-risk score," says Rakovitch. She says that the assay can pick out some women who are at a high risk of recurrence, but whom doctors might have considered to be low risk based on patient history and tumour characteristics.

SEARCHING FOR SIGNPOSTS

The search for a reliable measure to prevent surgery in the first place goes on. Any test, Hwang says, would probably involve a large array of markers that could be combined to form a cohesive picture. "We've taken the individual biomarkers as far as they can go and they're not giving us the answers we need," she says.

Thea Tlsty, a molecular pathologist at the University of California, San Francisco, and her colleagues have identified three proteins involved in cell proliferation that are associated with future aggressive breast cancers[5]. Tlsty's team found that of 1,162 women who had a lumpectomy for DCIS, those whose tissue was positive for all three biomarkers — COX-2, p16 and ki67 — had a 20% risk of developing an invasive cancer within 8 years. If they had none of the proteins, their risk dropped to 4%. "These markers indicate which pre-cancers are the baby, basal-like cancers, which are the most lethal and metastatic," she says. In unpublished research, Tlsty's group has subsequently identified several other potential biomarkers in proteins that coordinate cell death. Four prospective studies in Australia, the United States and the United Kingdom are further evaluating the trio of markers, Tlsty says.

Other biomarkers have also shown promise. Invasive breast cancers often stop the expression of tumour suppressor genes. One of those genes, called *SYK*, seems to be part of a genetic hub that determines which precancerous cells eventually metastasize. One study found that women who had altered expression of 55 genes that interact with *SYK* had reduced survival[6].

The search for circulating markers for early detection has proved frustrating at times, says Jeffrey Marks, a cancer cell biologist at Duke University. Marks and his colleagues selected 90 blood-based biomarkers, but none were useful in distinguishing cases of breast cancer from benign controls[7]. "They're very difficult to validate in independent populations," he says.

Some researchers are looking for signals that might reveal which DCIS lesions are associated with an increased risk of developing future invasive breast cancer. Andy Beck, a computational biologist at Harvard Medical School in Boston, Massachusetts, and his team are examining patterns of genomic alteration. Using data from DNA profiles of invasive breast cancers catalogued with The Cancer Genome Atlas, the group identified genomic locations that are most frequently copied or deleted in invasive breast cancer lesions. "We're basically saying that if it's not present in invasive cancer then it's not likely to be useful," says Beck.

In this case, the marker proved to be grimly robust. In a study of 271 patients, women with lesions that had extra copies in all three regions had a 17-fold higher risk of having a coincident invasive breast cancer compared with those women who had none[8]. The group is expanding the study to include about 20 chromosomal regions commonly altered in invasive breast cancer. In collaboration with Stanford University, Washington University and the Nurse's Health Study, the group is launching a study of 1,400 patients to predict the risk of recurrence or a subsequent invasive cancer over time.

Researchers have recognized that sheer genetic diversity within precancerous tissues may help to predict cancer formation and progression. As precancerous cells evolve and accumulate genetic and epigenetic alterations, they become more varied. Some studies have shown that diversity can predict progression. Marks is now studying the genetic diversity of the cells within DCIS lesions. In theory, if the DCIS has a more complex mosaic of cells, there is a stronger likelihood that one of them will develop into a more 'fit' cancer cell that can invade the surrounding tissue and metastasize.

Until scientists have a fuller understanding of which markers indicate an increased risk of developing invasive cancer, patients with DCIS will lack clarity about their future. For her part, Lapinski never went under the knife. Instead, she tracked down Hwang, who suggested that Lapinski join a three-month clinical study of the oestrogen-blocking drug tamoxifen. Lipinski was supposed to have surgery at the end of the trial, but she opted to forego the operation and continue with the tamoxifen, and, later, raloxifene. She checks in with Hwang twice a year for an examination and a mammogram. Although others see uncertainty in Lapinski's choice, she doesn't see it as a risky move. "Everybody has to make their own decision," she says. "It has to be comfortable for them." ■

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