

FEATURE STORY

Eluding Cancer

BY ERIK NESS

Breast cancer prevention meets success with new agents and a new thinking.

Few women get a more dramatic introduction to breast cancer prevention than Sharon Anderson. Nearly 15 years ago her identical twin Karen was nursing her fourth child when she noticed a lump in her breast. Karen's doctor thought it was a blocked milk duct, but after a few visits scheduled a mammogram. At the time doctors excised the lump, cancer had spread to 17 of 21 lymph nodes.

Karen lived in west Kansas but sought further treatment at the University of Kansas Medical Center, near her sister Sharon. After Carol Fabian, MD, director of the hospital's Breast Cancer Prevention Center, finished her first visit with Karen, she turned to Sharon. "Be here tomorrow at 8," she said firmly. "You are having your first mammogram."

Sharon Anderson was only 35 at the time, and no one had ever mentioned mammograms before. Now the veteran of four clinical trials, she's helping her daughter's generation fight cancer before it happens. One trial told her she carried the BRCA2 gene (a genetic mutation that markedly increases a woman's risk of breast and ovarian cancers), and she had the recommended oophorectomy (removal of the ovaries). She took the osteoporosis drug Evista[®] (raloxifene) for five years in the STAR (Study of Tamoxifen And Raloxifene) trial, which compared the effects of two breast cancer risk-reducing drugs. Now she's in a trial testing the aromatase inhibitor Aromasin[®] (exemestane).

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Despite four trials testing drugs known for side effects, she has never had a problem. "I never did like taking medicine. I guess I just think my body should be able to take care of itself," says Anderson, who also exercises regularly and watches her diet.

In this new era, complex cancers like breast cancer probably won't decrease as dramatically as cervical cancer, which may be practically eliminated with the new human papillomavirus vaccine. But the puzzling tangle of genetic and lifestyle factors that lead to breast cancer is finally starting to loosen. And the search for chemoprevention—drugs or nutrients that could slow down cancer or even prevent it altogether—is beginning to yield fruit.

Last year, leading British cancer epidemiologist Jack Cuzick, PhD, argued in the journal *Lancet Oncology* that it was time for oncologists “to catch up with the cardiologists,” who have cut deaths from heart disease in the United States by half using drugs like statins and a prevention mindset.

"Across the board it's better to prevent a disease," argues Werta McCaskill-Stevens, MD, of the Division of Cancer Prevention at the National Cancer Institute. “With time, we will hopefully come up with a combination of medical and lifestyle interventions that reduce the risk of breast cancer. It will be similar to treatment, so that an individual woman walks in and, depending on her profile, there are various options for her.”

What's Your Risk

Cancer prevention begins with figuring out your risk. You may have taken available online tests (www.cancer.gov/bcrisktool) that ask your age, how many immediate relatives have had breast cancer, age at menarche and age at first childbirth. Your answers get plugged into a complex equation developed by NCI biostatistics guru Mitchell Gail, MD, PhD, and out pops your likelihood of developing breast cancer in the next five years.

The strength of the Gail model is that it's accurate with very little information. (It works better for white women; the model is still being calibrated for other ethnic groups.) But if it tells you that five out of 100 women may develop breast cancer, it can't tell you which 5. Defining high risk is complex, but one commonly accepted measure of being at high risk of developing breast cancer in the next five years is a Gail score of 1.67 percent or greater. The Gail risk score is used in some prevention studies to determine eligibility.

A Star Is Born

After tamoxifen was released in the 1970s, doctors noticed breast cancer patients who took the drug, which inhibits estrogen activity, were less likely to develop a second cancer in the opposite breast. Research among high-risk women eventually revealed tamoxifen cut the risk of breast cancer in half over a period of five years. The well-known Breast Cancer Prevention Trial reported by the National Surgical Adjuvant Breast and Bowel Project found that of 13,175 high-risk women, 244 women in the placebo group developed breast cancer compared with 124 women taking tamoxifen.

In 1998, tamoxifen was approved for breast cancer prevention in high-risk women, though its main use has been to prevent recurrence of breast cancer.

Serious possible side effects—blood clots in older patients and a slightly increased risk of uterine cancer—alarmed high-risk, but otherwise healthy, women. In fact, for women over 65 with an only somewhat elevated breast cancer risk compared with the general population, the risk of side effects may actually outweigh the benefit.

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Evista works a lot like tamoxifen, so a massive comparison of the two began in 1999 involving nearly 20,000 high-risk women without a personal history of invasive cancer. The results of the STAR trial were released last year and showed Evista gave comparable protection with fewer blood clots and uterine cancers. Eli Lilly and Company submitted an application to the Food and Drug Administration in December 2006 for an additional approval of Evista for the reduction of breast cancer risk in postmenopausal women. The FDA's decision is expected before the end of the year.

"It's moving at the pace of government," says Victor G. Vogel, MD, director of the Breast Cancer Prevention Program at Magee-Womens Hospital in Pittsburgh. "It's regrettable that we aren't using the agents that we do have. There are a half million women taking Evista for osteoporosis, so they and their doctors are obviously comfortable with it."

Dr. Fabian says the STAR trial resulted in a draw. While Evista has fewer side effects overall, it doesn't seem to be as good as tamoxifen in reducing noninvasive breast cancer (ductal carcinoma in situ and lobular carcinoma in situ). "When you get a mixed message like this, it's very difficult to explain that to patients," she says.

Cheryl Pilate illustrates the problem. When her mother was diagnosed with breast cancer at an early age, Pilate was referred to Dr. Fabian's clinic for high-risk patients. At first everything looked clear, but then they began to see alarming changes in Pilate's breast tissue with a sampling procedure called random periareolar fine needle aspiration. The test results suggested she had 10 times the risk of her peers, which "broke through the little shell of denial that we all keep," says Pilate. "It really scared me."

Removing her ovaries was an option, but Pilate wanted to go through menopause naturally. She also considered tamoxifen. The side effects worried her, but her biggest concern was efficacy. "My lifetime risk was astronomically high. How does it help me to cut it in half?" She finally decided on a bilateral prophylactic mastectomy. "It was the best thing I've ever done in my whole life. I woke up in a state of elation and euphoria. It might seem radical to some, but to me it seemed

the least invasive.”

Next on the prevention horizon is a class of drugs called aromatase inhibitors, or AIs, which include Aromasin, Arimidex[®] (anastrozole) and Femara[®] (letrozole), for use in postmenopausal women who get estrogen not from their ovaries but as a byproduct of other processes in the adrenal gland and fat tissue (such as the breast). AIs interrupt this estrogen production, and based on how well they work with chemotherapy could provide an additional reduction in risk over tamoxifen and Evista.

The IBIS-2 prevention trial is an international study testing Arimidex for breast cancer prevention, and the ExCel trial in Spain, Canada and the United States is looking at Aromasin. STELLAR, a large-scale U.S. study comparing Femara and Evista, was expected to start recruiting in April. But the trial, expected to cost \$100 million, is currently on hold because of budget cuts to the National Cancer Institute.

“I don’t think there is any question but that the AIs are going to be more active than tamoxifen,” says Dr. Fabian. But she also wonders if enough high-risk women will be willing to live with potential side effects, such as bone loss and reduced libido or vaginal dryness. “That’s even worse than hot flashes,” she says. Designing drugs with fewer side effects, or that can be taken for shorter periods of time, is a significant challenge. The long-term effects of AIs are not yet known since they have not been in use as long as tamoxifen.

Optimal Prevention

Using clues called biomarkers, scientists hope to improve their powers of prediction. Single genes like BRCA1 and BRCA2 are clear biomarkers. Others that suggest breast cancer risk include mammographic density (how much of the image is white) and the level of hormones, such as testosterone, estradiol and the growth hormone IGF-1. High-risk clinics also perform biopsies that look for what’s called atypical hyperplasia—essentially too many cells—which can be a precursor to breast cancer.

A less-invasive biomarker would be welcomed, but what’s really needed is one that reliably indicates risk and response to treatment. Dr. Fabian is confident we’re within a few years of being able to use biomarkers like atypical hyperplasia to reduce the participant number, time and cost of breast cancer prevention trials. “We have this vast array of things that are promising,” she says, but “you can’t spend \$200 million on each one.”

And the roster of potential agents for breast cancer prevention alone is huge. Among those working their way through clinical trials are arzoxifene (works like tamoxifen); the statin Zocor (simvastatin); anti-inflammatory agent Clinoril (sulindac); and all three AIs. Dozens more have caught investigators’ eyes. And many potential prevention regimens combine several compounds and may even work in combination with modified hormone replacement therapy.

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cardiovascular disease into what we can do and know now for preventive oncology. ❏

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“I think it’s all about the agent,” says Dr. Vogel. “We’re on our way to finding the optimal agent, but we haven’t found it yet.”

From a public health perspective, Dr. McCaskill-Stevens says prevention is extremely important and physicians must have a medical intervention. Prevention also means oncologists and their patients need to occasionally pull back from the relentless pursuit of malignancy and see the whole patient.

“More than 75 percent of women who get breast cancer today will never die from their disease,” says Dr. Fabian. “We have to seriously think about prevention of other diseases that we might induce with treatment. Prevention and survivorship are part of the same continuum.”

Researchers have established that the prevention paradigm works with early detection, screening interventions and reducing risk factors, says Dr. Vogel. “It’s just a matter of translating what we already do and know for cardiovascular disease into what we can do and know now for preventive oncology.”

Part of the challenge is getting the medical finance industry to pay for preventive services. “As soon as you start paying for these services, doctors will start providing them,” says Dr. Vogel. “The pressure for mammographic screening to be used across the board did not come from the medical community. It came from the advocate community.”