Stopping Breast Cancer Before It Starts

Greater understanding of risks and benefits may convince more women to take SERMs

More than 230,000 women are diagnosed with breast cancer in the United States annually. Of that number, “there are probably about 30,000 cases that wouldn’t have to happen if women at high risk of the disease took a pill a day,” says Victor Vogel, MD, director of breast medical oncology/research at Geisinger Cancer Institute in Danville, PA.

The pills to which Vogel refers are selective estrogen receptor modulators (SERM), which compete with estrogen to bind estrogen receptors (ER), stemming the growth of ER-positive breast cancer, which accounts for about 75% of breast cancers. The best-known SERMs—and the only drugs approved in the United States to reduce the risk of breast cancer—are tamoxifen and raloxifene (Evista; Eli Lilly).

The National Surgical Adjuvant Breast and Bowl Project (NSABP) P-1 and P-2 breast cancer prevention trials, which involved more than 33,000 women, and other studies have shown that women with an increased risk of developing breast cancer can cut their risk almost in half by taking tamoxifen or raloxifene for 5 years. The benefit continues for at least 5 years after therapy ends, according to recent follow-up studies.

Despite these findings, less than 1% of women eligible to take SERMs to reduce their breast cancer risk actually do so. One reason, Vogel says, is that primary care physicians “don’t seem to feel comfortable with the whole notion of breast cancer risk assessment and risk reduction.”

Concern about serious but rare side effects, primarily endometrial cancer (tamoxifen) and blood clots (both drugs), has also been a barrier to SERM use, says Powel Brown, MD, PhD, chairman of the Department of Clinical Cancer Prevention at The University of Texas MD Anderson Cancer Center in Houston. “There’s been a huge amount of discussion about the side effects but not an understanding and appreciation that for some women, the benefit greatly outweighs the risk,” he says. “We need to get that message out.”

Updated guidelines for the use of medication to reduce breast cancer risk, issued in recent months, may help. The U.S. Preventive Services Task Force released a draft recommendation in April suggesting that doctors talk about the possible harms and benefits of taking a risk-reducing medication with women ages 40 to 70 who are at increased risk for breast cancer, have never had the disease, and have no history of blood clots.

The UK’s National Institute for Health and Care Excellence (NICE) guidelines, issued in June, go a step further, recommending that clinicians “offer either tamoxifen or raloxifene for 5 years to postmenopausal women with a uterus and at high risk of breast cancer unless they have a past history or may be at increased risk of thromboembolic disease or endometrial cancer.”

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The American Society for Clinical Oncology (ASCO) recommendations, released in July, say that tamoxifen use should be discussed with women age 35 and older who are at increased risk of breast cancer. In addition, for postmenopausal women with an increased risk of the disease, raloxifene and exemestane should be discussed as options, the guidelines say. (Exemestane, an aromatase inhibitor, decreases the production of estrogen. Although it is used for breast cancer treatment, exemestane is not approved for risk reduction.)

RATING RISKS

Who is an ideal candidate for SERM therapy? That is not easy to answer, says Heidi Nelson, MD, MPH, a research professor of medical informatics and clinical epidemiology and medicine at Oregon Health & Science University in Portland. Ideal candidates, she says, should be at high risk for breast cancer and at low risk for adverse effects, but no models exist to predict who meets both of those criteria.

Several tools can help patients and their physicians calculate breast cancer risk, including the National Cancer Institute’s Breast Cancer Risk Assessment Tool and the International Breast Cancer Intervention Study tool. Both account for critical factors such as age, family history, and previous breast biopsies. However, such models perform only slightly better at predicting breast cancer in an individual woman than consideration of age alone, says Nelson.

Improvements in risk assessment will likely come from molecular diagnostics. For example, researchers recently discovered genetic markers that may help determine which women might respond best to SERMs. Using DNA from the NSABP trials, they analyzed 500,000 single-nucleotide polymorphisms (SNP) and discovered that two SNPs—one in ZNF423 and the other near CT50—occurred more often in women who developed breast cancer. Women with the variant SNP in ZNF423 and the wild-type SNP near CT50 were nearly six times less likely to develop breast cancer while taking SERMs than women lacking those alleles.

The early findings must be confirmed, says James Ingle, MD, professor of oncology at the Mayo Clinic in Rochester, MN, the study’s lead author, but “if patients were more confident that they are likely to get a benefit from SERMs, that would be a huge step for prevention.”

Tamoxifen (red, white, and blue) competes with estrogen to bind to the estrogen receptor (aqua) and stems the growth of ER-positive breast cancer. Taking tamoxifen or raloxifene for 5 years can reduce the risk of developing the disease by nearly half, with the benefit extending for 5 more years.
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Updated version
Access the most recent version of this article at:
doi:10.1158/2159-8290.CD-ND2013-019

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