The Lack, Need, and Opportunities for Decision-Making and Informational Tools to Educate Primary-Care Physicians and Women about Breast Cancer Chemoprevention

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Abstract

This perspective on Vogel et al. (beginning on page 696 in this issue of the journal) examines tamoxifen and raloxifene prescription patterns and why these agents are little used for breast cancer prevention despite their effectiveness in definitive trials, Food and Drug Administration approval, and American Society of Clinical Oncology Guidelines Committee endorsement for this purpose. The complexity of weighing the positive and negative aspects of the drugs and estimating net benefit is discussed, as is the need for informational resources such as interactive Internet-based tools to allow better individualized decisions about the options for chemoprevention.

Despite results of the Breast Cancer Prevention Trial (BCPT, P-1; ref. 1) and the Study of Tamoxifen and Raloxifene (STAR, P-2; ref. 2) showing that the selective estrogen-receptor modulators (SERM) tamoxifen and raloxifene are effective breast cancer prevention agents and despite their U.S. Food and Drug Administration (FDA) approval and endorsement by the American Association of Clinical Oncology Guidelines Committee (3) for this purpose, these agents are infrequently prescribed for chemoprevention. Why? This perspective will examine the complex reasons and suggest resources that may help in overcoming them.

Completed and published in the United States, the large BCPT and STAR show that women with at least a 1.67% 5-year risk (as estimated by the Gail model; ref. 4) who take tamoxifen or raloxifene about halve their risk of developing breast cancer (1, 2). The Gail model shows that the average woman reaches this level of risk by the age of 60, and National Cancer Institute estimates show that more than 10 million women might meet the risk criteria approved by the FDA for use of these preventive agents (5). This careful analysis, however, shows that the number of these women likely to experience a net benefit is limited somewhat by side effects. So, have these agents been widely adopted? If not, why not? Is there a widely available tool that can be used to identify which of the 10 million plus women eligible to take an approved SERM are likely to experience a net benefit?

Indeed, these agents are not widely used for chemoprevention, although they were approved by the FDA for breast cancer risk reduction (6) in 1998 (tamoxifen) and 2007 (raloxifene). Exact figures about how frequently tamoxifen and raloxifene are used for chemoprevention are not available, but an estimate can be inferred. Figure 1 shows the number of prescriptions filled in the United States for tamoxifen and raloxifene from 1995 through 2008. This is an inexact measure of use for chemoprevention because the indications for prescriptions of these drugs are complex and unrecorded and there may be other influences on use, such as the replacement of adjuvant tamoxifen by adjuvant anastrozole after the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial was reported in 2001 and led to FDA approval of adjuvant anastrozole in 2002. Nonetheless, in 1999 and 2000 (after the 1998 approval of tamoxifen for chemoprevention but before ATAC results were reported), tamoxifen use increased only slightly, suggesting that few women (fewer than 1 million, probably far fewer) started taking tamoxifen for chemoprevention. Certainly, the number was far lower than the National Cancer Institute estimate of 2.4 million women who have age and risk characteristics suggesting they might benefit from tamoxifen (5). This conclusion is supported by a recent report from a survey conducted from 2000 to 2005 showing that only 0.2% of women ages 40 to 79 (~120,000 women) were taking tamoxifen for chemoprevention (7). In a similar vein, there was no increase in raloxifene use, which was already decreasing and continued to do so at the same rate, in 2007 and 2008 after the first report of the STAR (in 2006) and FDA approval of raloxifene (in 2007) for breast cancer risk reduction. Again, this overall pattern of use makes it very unlikely that large numbers of women started to use raloxifene for reducing their risk of breast cancer.
Why have tamoxifen and raloxifene not been adopted more widely? The amount of research addressing this question is modest but illuminating. A 2002-2004 survey of 350 primary-care physicians who were members of the American Medical Association found that only 27% had prescribed tamoxifen for breast cancer risk reduction in the previous year (7). An important predictor of a tamoxifen prescription for chemoprevention was the perception that the drug’s benefit in preventing breast cancer would outweigh the drug’s risks—the physicians who were unsure of this balance were much less likely to recommend or prescribe tamoxifen. Other surveys also show that a minority of primary-care physicians were prescribing tamoxifen or raloxifene for breast cancer prevention (8, 9). A study in California (10) found that the most frequent barriers to counseling were “not enough time” (40%) and “insufficiently informed about risk-reduction options” (19%). Concerns about serious side effects including endometrial cancer also were important barriers, and a perceived weak or unfavorable risk-benefit ratio for an individual patient made taking a SERM for chemoprevention unacceptable (11–13). These studies did not quantitatively explore patients’ accuracy in understanding the risks and benefits of either approved SERM.

In addition to the easily defined side effects such as endometrial cancer and stroke, very important but less quantifiable issues of quality of life play a role in the decision to use a SERM for chemoprevention. These issues were carefully evaluated in both the BCPT (14) and STAR (15). In the STAR, there were no significant differences between the tamoxifen and the raloxifene groups in patient-reported outcomes for physical health, mental health, and depression. The tamoxifen group reported better sexual function. Although mean symptom severity was low overall in this trial’s population of postmenopausal women, the tamoxifen group reported more gynecologic problems, vasomotor symptoms, leg cramps, and bladder control problems, whereas the raloxifene group reported more musculoskeletal problems, dyspareunia, and weight gain.

These symptoms are often reported as indices, with numerical values (or changes in these values) that are basically uninterpretable to most health professionals and patients alike. Nonexperts in these measures are challenged by how to weigh and convey them in deciding seriously whether or not to recommend or take a SERM for chemoprevention.

Weighing the positive and negative aspects of these therapies and producing an estimate of net benefit is a complex process requiring an understanding of the baseline risks of multiple end points and the relative-risk effects of tamoxifen and/or raloxifene. It is probable that few physicians and patients who engage in this process are doing so in a thoroughly informed way.

Tools to make the results of the BCPT and STAR more understandable to health professionals and women are clearly needed. These tools must allow easily accessible estimates of individualized baseline risks (on the basis of age, race, health history, etc.) not only of breast cancer but also of other health problems such as endometrial cancer, thrombotic events, stroke, and fracture. Such tools also must produce estimates of the relative and absolute changes in these multiple risks in association with tamoxifen or raloxifene treatment. A tool of this type in the form of a complex set of tables was produced on the basis of BCPT data. Published in 1999, it appeared in the Journal of the National Cancer Institute rather than in a journal with a larger primary-care readership, and it is unclear whether many primary-care physicians are even aware of it. In the present day, such a tool could be implemented on the Internet, which could enhance its availability and “friendliness” to users. The Gail model has been implemented on the web as The Breast Cancer Risk Assessment Tool (16), and this implementation is an example of a very useful interactive tool. Its scope, however, is limited to estimating a woman’s absolute risk of invasive breast cancer (no other diseases) over the next 5 years and up to age 90, or the lifetime risk (for comparison, the tool also can calculate average 5-year and lifetime risks based on a user’s age), and it has no ability to examine the effects of tamoxifen or raloxifene on risk. A tool or tools that would allow both health professionals and women to better understand and communicate some of the more-complex end points, such as more subjective measures relating to quality of life, are crucially needed.

Numerous tools are emerging to assist in the education, communication, and decision-making of patients and clinicians (17, 18). For example, the widely used tool Adjuvant! Online (19, 20) interacts with users, allowing them to enter information and to select different treatment scenarios. It can produce numerical estimates of the risk of relapse and mortality and allows users to review treatment
guidelines. It also contains extensive text information and medical illustrations. These materials allow users to better understand the state of the evidence for various adjuvant treatments. Adjuvant! Online presents and integrates complex information. It is designed for the very specific encounter of a specialist talking with a patient about adjuvant therapy. Similar tools for use in chemoprevention would have many of the same characteristics but would be designed for the encounter between a primary-care specialist and a woman or to prepare women for such encounters. Such tools would allow the user to review the multiple end points, including some of the complex and not always easily explained quality-of-life end points, which are affected by tamoxifen and raloxifene and by new chemopreventive agents that will come into use.

References


After the huge investment in the definitive chemoprevention trials of tamoxifen and raloxifene, a realistic hope, one might imagine, is that a relatively modest but crucial amount of time, effort, and money will be invested in developing interactive, Internet-based decision-making tools that will allow health professionals and women to understand the results of the trials and make well-informed individualized decisions about whether SERM chemoprevention is the right choice for them.

Disclosure of Potential Conflicts of Interest

P.M. Ravdin has an ownership interest in Adjuvant! Online.

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