Making Good Decisions about Breast Cancer Chemoprevention

W
omen worry about many things. When the worry is about health, breast cancer tops many women’s lists. The fear is not irrational, and it often has a personal face. Nearly 1 in 10 women has a first-degree relative with breast cancer, and many more know a close friend or acquaintance with the disease (1). Public health agencies and advocacy groups actively promote breast cancer awareness. Popular magazines publish heart-rending stories of young women with breast cancer (2). Thus, it is not surprising that women, especially young women, have exaggerated perceptions of their risk for breast cancer (3, 4).

Worry can motivate behavior to prevent disease, but it can also cloud perspective. A community survey found that 23% of women expressed interest in breast cancer chemoprevention (5). Worry about breast cancer was the strongest predictor of interest, but there was no association between interest and objectively estimated personal risk. Smokers were nearly twice as likely as nonsmokers to express interest in chemoprevention. Mortality rates underscore the irony of this finding. Of 1000 fifty-year-old women who smoke, 4 will die of breast cancer in the ensuing 10 years, whereas 13 will die of heart attacks, 10 of lung cancer, and 6 of stroke (6).

Clinicians need perspective, too. Specialists may neglect competing diseases as they focus attention on what can be done within their area of interest. Primary care clinicians must respond to women’s concerns about breast cancer and be proactive in helping them to identify the most promising opportunities to improve or maintain health. Setting priorities among the many interventions that compete for time in the clinical encounter is difficult—and missing opportunities is justifiably a source of worry for clinicians. Furthermore, clinicians are increasingly being asked to involve patients in decisions that have no clear best choice. Evidence suggests that clinicians are not always meeting this challenge effectively (7).

It is against this backdrop that women and their clinicians receive the latest recommendations for chemoprevention of breast cancer from the U.S. Preventive Services Task Force (USPSTF) in this issue (8). The recommendations are accompanied by a review from Kinsinger and colleagues (9) of the four trials that have addressed the use of selective estrogen receptor modulators, specifically tamoxifen and raloxifene, for primary prevention of breast cancer. Findings were positive in two of the trials and negative in the other two. The review focuses largely on the results of the positive trials, noting that they were highly consistent with the reduced incidence of contralateral breast cancer reported in trials of adjuvant tamoxifen therapy (10).

The National Surgical Adjuvant Breast and Bowel Project P-1 Study, known as the Breast Cancer Prevention Trial (BCPT) (11), enrolled women with an estimated 5-year risk greater than 1.66%, an arbitrarily chosen eligibility criterion that approximates the average risk in a 60-year-old woman. The BCPT was terminated early after finding a relative reduction in breast cancer incidence of 49% and an absolute risk reduction of just over 20 cases per 1000 women taking tamoxifen over 5 years. The effect was limited to estrogen receptor–positive tumors. The BCPT also documented significant harms associated with tamoxifen, including an increased risk for endometrial cancer, deep venous thrombosis, pulmonary embolism, and stroke, especially in women older than 50 years.

The Multiple Outcomes of Raloxifene Evaluation (MORE) trial (12) found breast cancer incidence to be 76% lower with raloxifene than with placebo, with an absolute risk reduction of 8 cases per 1000 women over 40 months. Again, the effect was limited to estrogen receptor–positive tumors, for which relative risk reduction was 90%. The two trials with negative findings were conducted in Europe. The Royal Marsden Hospital Chemoprevention Trial (13) and the Italian Tamoxifen Prevention Study (14) compared tamoxifen with placebo and failed to find a reduction in breast cancer incidence. Differences in study populations and conduct of the trial are cited as explanations for the discrepant results. All women in the Royal Marsden trial had a family history of breast cancer. Participants in the Italian study were younger than those in other trials. The use of exogenous estrogen was allowed in the European trials but not the BCPT. Adherence was better and duration of tamoxifen therapy was longer in the BCPT.

On the basis of this review of the evidence, the USPSTF recommends against widespread use of chemoprevention for patients with a low or average risk for breast cancer. The USPSTF recommends discussing chemoprevention with selected patients at high risk for breast cancer and at low risk for the most serious adverse events. This is a more conservative position than might have been expected when the BCPT was terminated and the U.S. Food and Drug Administration approved tamoxifen in 1998 for use in women aged 35 years and older with a 5-year risk greater than 1.66%. The recommendations reflect the considerable potential harms associated with serious adverse events induced by tamoxifen. Considering the benefits and harms, the USPSTF relied on an analysis that applied equal weight to cases of breast cancer that were prevented and to cases of endometrial cancer, pulmonary embolus, and stroke induced by tamoxifen (15). However, the responses of individual women to tradeoffs between these good and bad outcomes are likely to vary considerably.

The current evidence leaves many questions unanswered. Do chemoprevention agents prevent cancer or treat very early cases? How long does the effect of lowered incidence of breast cancer persist after taking a chemopre-
ventive drug for 5 years? Will breast cancer cells develop resistance to tamoxifen? Together, these issues beg the question not directly addressed by the trials and still not answered: Does chemoprevention reduce breast cancer and all-cause mortality and, if so, by how much?

This lack of evidence for the long-term effectiveness of chemoprevention is particularly troubling, given that the recommendations focus on its potential appropriateness for younger high-risk women. The differential effect of chemoprevention using tamoxifen or raloxifene on estrogen receptor–positive and estrogen receptor–negative tumors raises additional as-yet-unanswered questions about the biology and early natural history of breast cancer. The answers to these questions are particularly relevant for younger women in whom breast cancer is more likely to be estrogen receptor-negative at the time of diagnosis.

The USPSTF recommendations present two serious challenges for clinicians who care for women across the spectrum of age and breast cancer risk. First, clinicians must respond to the misinformed and mitigate the worry that may cloud perspective and create demand for chemoprevention when the potential harms far exceed the benefits. Second, clinicians must identify and engage the uninformed for whom, because of their risk profile and personal preferences, chemoprevention holds potential promise.

Risk estimation and communication are at the center of both challenges. The USPSTF refers to the model developed by Gail and colleagues (16) as one tool for estimating risk. The BCPT used the Gail model to estimate the 5-year incidence of breast cancer for patient accrual on the basis of a woman’s age, number of first-degree relatives with breast cancer, nulliparity or age at first birth, number of breast biopsies, pathologic diagnosis of atypical hyperplasia, and age at menarche. For women whose worry results from an exaggerated perception of risk, such estimates may provide reassurance, but the source of anxiety may be more complex than simple misinformation (17). Risk estimates specific to estrogen receptor–positive types of breast cancer would be more helpful. Furthermore, a perspective for good decision making requires 5-year and lifetime mortality estimates not provided by the Gail model. Just as important are estimates over varying periods of incidence and mortality for competing conditions, especially those made more likely by chemoprevention. For example, a stroke or pulmonary embolus confers a high risk for immediate physical disability and death. A diagnosis of breast cancer, distressing as it may be, does not. Therefore, a good decision about chemoprevention requires attention to the timing of harms and benefits as well as to the varied individual preferences concerning any tradeoffs between them.

Given the complexity of the decision and related communication tasks, the USPSTF recommendation to discuss chemoprevention with selected patients raises more questions for clinicians than it answers. How do you help diffuse a patient’s worry so that it does not cloud judgment? How do you help a woman clarify how she feels about the harms and benefits as well as their timing? How do you help younger women deal with the uncertainty about the long-term impact? When should the discussion be broadened to include other strategies for prevention, including prophylactic surgery, the prospect of waiting for more promising chemopreventive agents, or participation in current randomized trials? Evidence strongly suggests that well-designed and rigorously evaluated decision aids could help with these questions and significantly improve the quality of the decisions made. Better appreciation of current medical knowledge and uncertainties could also foster participation in trials (18, 19).

Making fateful decisions that depend on medical science as well as highly personal judgments about how future illness will affect quality of life is difficult, at best. Neither doctor nor patient can do it alone. For both, the stakes are high. With breast cancer chemoprevention, clinicians and patients need to understand the limits of what we know and what we can control about the future. Breast cancer will happen with and without preventive measures, as will serious conditions, such as pulmonary embolus and stroke. Women and doctors who work at making good decisions together will be far more likely to make the best use of what current medical science has to offer. They may also worry less about the future.

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