Is Tamoxifen Advertising a Public Service or a Public Nuisance?

In the March/April 2000 issue of **ecp**, Drs. Press and Burke write that "interim results from two European tamoxifen trials have not shown the substantial reduction in risk seen in the American trials."[1] It is important to note that the British Royal Marsden Hospital trial was designed and initiated as a pilot feasibility trial.[2] Published results of this pilot trial are derived from an interim analysis at a median follow-up of 70 months. Participants were younger women who had a stronger family history of breast cancer, and 26% of the participants used hormone-replacement therapy concurrently with tamoxifen. It is not clear why the study produced negative results, but more of the British women may have been at greater risk for *BRCA1* mutations and development of estrogen receptor–negative tumors that were not influenced by tamoxifen use. The Italian study enrolled a low-risk population of women, of whom 48% had bilateral prophylactic oophorectomies before entering the trial; only 41 cases of breast cancer had developed at a median follow-up of 46 months.[3] Adherence to the study medication was poor, and 26% of participants left the trial early; as a result, accrual to the trial closed prematurely. Because of these major concerns with their design and conduct, the European trials cannot be regarded as refuting the Breast Cancer Prevention Trial.[4]

It is not clear to me why Drs. Press and Burke regard the Astra Zeneca direct-to-consumer approach "disturbing." I am well aware that many women overestimate their risk for developing breast cancer,[5, 6] but an invitation for quantitative risk assessment improves, rather than worsens, the situation. For women 35 to 59 years of age, risk assessment tools are available to identify those at increased risk. The National Cancer Institute has developed a computerized risk assessment tool that performs accurate risk projections for women with several risk factors for breast cancer. The Astra Zeneca ad directs women to this "risk disk," which calculates and prints 5-year and lifetime projected probabilities of developing invasive breast cancer and can be used to identify women who are at increased risk. At most, the modified Gail model[7] used in the risk disk will identify only 20% to 30% of women as having a risk greater than 1.66% in 5 years. The U.S. Food and Drug Administration has been appropriately conservative in approving tamoxifen for risk reduction only in women who meet that eligibility criterion.

Although I can certainly concur with Drs. Press and Burke's contention that all experts would agree that this treatment is inapplicable for most women in the US, tamoxifen is nevertheless appropriate for women who

have increased risk for developing breast cancer, have no contraindications to its use, and understand the risks and benefits associated with using it for risk reduction.

That is precisely what the ad says: "Nolvadex is not for every woman at high risk." The first step is risk assessment, and the ad appropriately calls that fact to women's attention. The ad is, therefore, a public service rather than a "public health concern."

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Potential Conflict of Interest

Dr. Vogel is a member of the Astra Zeneca speakers bureau through Discovery International, Inc.

Further Information

Copies of the risk disk can be obtained from the National Cancer Institute Web site at http://cancertrials.nci.nih.gov/forms/ctRiskDisk.html.

References

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THE AUTHORS RESPOND

As Dr. Vogel notes, and as we indicated in our commentary, it is uncertain why the results of the U.K. tamoxifen trial differ from those of the U.S. trial. The recruitment criteria for the U.K. trial may have included a higher proportion of women with BRCA1 *mutations, who might be less likely to benefit from tamoxifen because of their higher risk for estrogen receptor–negative tumors. We also agree with Dr. Vogel that aspects of study design or participant adherence may have contributed to the negative results of the Italian tamoxifen trial. Although it is fair to say that the European trials do not refute the U.S. trial results, it is also fair to say that they have failed to provide the corroborating evidence that might have been expected.*

More to the point, the U.S. trial leaves many important questions about tamoxifen use unresolved. One, as already noted, is the utility of tamoxifen in women who carry BRCA1 *mutations. This uncertainty speaks to the difficulty in determining which women among those at increased risk might actually benefit from tamoxifen prophylaxis, and it underscores a reason for our concern about the ad: As Dr. Vogel noted, if the ad is interpreted correctly by consumers and health care providers, it is precisely these younger women with a family history of breast cancer who are most likely to achieve the risk level indicated by the number 1.7—the number implied by the ad to be an indicator for tamoxifen use.*

Other uncertainties, noted in our commentary, include the long-term risks and benefits of tamoxifen use and the risks of forgoing estrogen in favor of tamoxifen prophylaxis. This latter point is of particular importance for most women with the 1.7 score—average-risk women, most of whom achieve this score at age 60.

We agree that the U.S. tamoxifen trial points to a possible important benefit of tamoxifen for some women, but we do not feel it should yet be considered established therapy for any group. We are thus strong supporters of the current Study of Tamoxifen and Raloxifene (STAR), in which tamoxifen is being compared with raloxifene as a means for preventing breast cancer in women at high risk. This trial is an example of the appropriate response to powerful research results, such as those of the U.S. tamoxifen trial, that raise as many questions as they answer: continued research. We believe that entry into a well-designed clinical trial remains the best option for women at high risk and who are interested in this potentially beneficial therapy, because it provides treatment in the context of objective measurement of outcomes.

We would like to emphasize, however, that the focus of our commentary was not on tamoxifen per se but rather on the inappropriateness of direct marketing of tamoxifen to consumers. Although we agree with Dr. Vogel that current data now offer the means to identify women with an increased risk for breast cancer, we are far less certain about the benefits of the risk assessment process, particularly in the format provided by the National Cancer Institute risk assessment tool (the "risk disk") highlighted in the ad. This tool, available by calling an 800-number and on the World Wide Web, calculates a woman's risk for breast cancer in the next 5 years and over her lifetime, taking into account her age, reproductive history, history of breast biopsies, and partial information about her family history of breast cancer.

Although it is true, as Dr. Vogel points out, that the risk tool will provide most women with a risk that is lower than 1.7, the reassurance resulting from this calculation is likely to be limited. This is because the risk tool presents the woman's personal risk in comparison to a baseline risk estimate. We are not sure of the source of the baseline risk calculations because the risk tool does not specify it. However, by our calculations, the baseline estimate represents the risk for a woman who had menarche at age 15, her first pregnancy at age 19, and no other risk factors for breast cancer: In other words, the baseline comparison is an exceedingly atypical "no-risk woman," and nearly all women will have a risk that is higher than that. Although few will reach a 1.7 level, it seems reasonable to hypothesize that what women will take away is that they have an elevated risk compared with the risk-disk "baseline" woman. This perception of increased risk will be true even for most women who a geneticist would consider to be at average risk. We doubt that this exercise will be reassuring to most women.

It should also be noted that the Gail model—on which the risk assessment tool is based—uses only partial family history data, specifically the number of first-degree relatives with breast cancer (categorized as 0, 1, or 2 or more relatives affected). This coding strategy leads to a notable weakness in the model that, in our view, makes it an inappropriate method for assessing risk status in women with a family history of breast cancer. The model accords equal weight to modest or irrelevant family history (e.g., a mother who develops breast cancer at age 80) and to significant family history (e.g., a mother who develops breast cancer at age 30) and fails to take into account significant family history in second-degree relatives. Again, with regard to this advertising campaign, data indicating that the Gail model overestimates risk in younger women become of particular concern as well.

The ad does indeed say that tamoxifen is "not for every woman at high risk." But, as we attempted to show in our commentary, many elements of the ad suggest otherwise, beginning with the choice of a direct-to-consumer advertising strategy initiated by an ad in the most widely circulated newspaper supplement in the United States. This very placement implies that this drug may be applicable to a large segment of the female population.

When data on U.S. women's exaggerated and painful fears about breast cancer are taken into account, the advertisement seems even more questionable. Information is not always knowledge, but unfortunately, authoritative-seeming misinformation can still be all too powerful to the alarmed and cleverly targeted consumer.

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