Re: Tamoxifen Prevention of Breast Cancer: an Instance of the Fingerpost

In their commentary on tamoxifen, Lippman and Brown ([1], p. 1813) cite figures from Fisher (2) and state that “these figures demonstrate that tamoxifen prevention potentially could impart a substantial net benefit to the public health.” In light of the article presented by Gail et al. (3) in the same issue of the Journal and some of our own calculations given below, we wish to offer a different perspective.

According to Fisher’s cited commentary (2), approximately 29 million women in the United States would meet the eligibility criteria for the Breast Cancer Prevention Trial (BCPT) (4), and in this group of 29 million, 1.4 million cases of breast cancer might be expected during the course of 5 years, of which 700,000 would potentially be prevented by prophylactic use of tamoxifen. First, there are not 1.4 million cases of breast cancer in the entire population of U.S. women over a 5-year period. For the past 5 years, there have been between 175,000 and 185,000 cases of breast cancer per year (5). Second, not all breast cancer cases are going to occur among women eligible for tamoxifen chemoprevention. Women were eligible for the BCPT if they fell into one of the following categories (4): aged 35–59 years with a 5-year risk of at least 1.67% (the 5-year risk of the “average” 60-year-old U.S. woman) according to the model of Gail et al. (6), age greater than or equal to 60 years, or history of lobular carcinoma in situ.

Because of concern over whether all healthy women 60 years of age and older should be advised to consider tamoxifen (7), the U.S. Food and Drug Administration (FDA) indications for tamoxifen chemoprevention are slightly different from the BCPT eligibility criteria: aged 35 years of age or older and a 5-year risk of at least 1.67%. In the Nurses’ Health Study cohort, only 30% of women aged 60–69 years had a 5-year risk of 1.67% or higher, as estimated by the model of Gail et al. In this cohort, among women aged 35–69 years who developed breast cancer during a 5-year period, fewer than one-quarter of cases occurred in women who would have been eligible for tamoxifen under the FDA indications. For several important reasons, therefore, it is misleading to state that 50% of 1.4 million cases of breast cancer during a 5-year period could be prevented by tamoxifen.

More important, the statement by Lippman and Brown (1) that there might be substantial public health gains from prophylactic tamoxifen use disregards the central message of the analysis by Gail et al. (3). This analysis shows that it is unlikely that chemoprevention with tamoxifen will lead to substantial public health benefits. Indeed, the calculations by Gail et al. (3) indicate that widespread tamoxifen use would lead to net public health losses precisely in the very large segment of the general population that contributes the bulk of breast cancer cases, i.e., women aged 50–79 years (both black and white) with intact uteri and with breast cancer risk that is not very different from “average.” Benefit outweighs harm for white women aged 50–59 years and 60–69 years only at very high levels of breast cancer risk (≥3.5% for women 50–59 years of age and ≥6.5% for women 60–69 years of age). The proportion of white women in these age-risk groups is exceedingly small in the general population, unlike their representation in the BCPT. In the Nurses’ Health Study cohort, less than 1% of women aged 50–59 years had a 5-year breast cancer risk greater than or equal to 3.5% as estimated by the Gail et al. model; less than 0.5% of women 60–69 years of age had a 5-year risk greater than or equal to 6.5%. Less than 4% of all breast cancer cases that occurred in the cohort over a 5-year period arose among these high-risk women. For black women, who face higher risks of stroke, pulmonary embolism, and deep-
vein thrombosis than white women, tamoxifen use is likely to cause a net loss of public health in nearly all age-risk groups.

Both the commentary of Fisher (2) and that of Lippman and Brown (1) rely on unrealistic estimates of numbers of cases of breast cancer prevented to make their argument for public health benefits of tamoxifen. Fisher (2) even cited a possible reduction of 1 million cases of breast cancer in 5 years, if 2 million cases were to occur among women eligible for the drug. The analysis by Gail et al. (3), while subject to some uncer-

As is evident by an examination of popular magazines, Zeneca is currently engaged in an extensive, consumer-directed, marketing campaign for breast cancer chemoprevention with tamoxifen. Clearly, more attention to the risk/benefit calculations of Gail et al. is needed before prophylactic use of this drug becomes widespread.

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REFERENCES

(7) Oncologic Drugs Advisory Committee. 58th meeting. Bethesda (MD): Food and Drug Administration, Center for Drug Evaluation and

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RESPONSES

The last sentence of the letter of Rockhill et al. states, “more attention to the risk/benefit calculations of Gail et al. is needed before prophylactic use of this drug [tamoxifen] becomes widespread.” We agree. The first sentence in their letter quotes our commentary (1) by including the important word “potentially” after the word “prevention.” Despite this clearly qualified statement, they wished to offer a different perspective. We wish they also had put this important issue (net public health impact of tamoxifen) into the proper perspective. Their letter missed the major theme of our commentary (i.e., the proof of the principle of cancer chemoprevention), which also included many other major issues, such as the development of promising new agents (e.g., those involving new selective estrogen receptor modulators). The letter of Rockhill et al. sharply criticizes Dr. Fisher’s published stance on tamoxifen’s net public health impact (2). We believe that it is appropriate to leave it to Dr. Fisher to defend his position.

Rockhill et al. did not acknowledge that the net public health issue appeared in the section entitled “Unresolved [italics added] Tamoxifen Prevention Issues.” We never stated categorically that tamoxifen will provide a net public health benefit. Several other misinterpretations and overinterpretations in the letter of Rockhill et al. include the statement that tamoxifen use for African-Americans “is likely to cause a net loss of public health in nearly all age-risk groups,” ignoring the paper by Gail et al. (these estimates are “subject to greater uncertainty”) (3), an accompanying editorial (these risk/benefit rates are misleading) (4), and the American Society of Clinical Oncology technology assessment (“It is reasonable to apply the same criteria for tamoxifen use across all ethnic groups . . . .”) (5); the unfounded implication that we think tamoxifen is risk-free prevention for every woman, ignoring our painstaking discussions of the risks (1); and a total disregard of certain favorable indications, such as for women who have had hysterectomies (e.g., favorable risk–benefit ratios as stated by Gail et al. for every age-risk category of such women 35–59 years old) (3).

According to Rockhill et al., the Nurses’ Health Study (NHS) indicates that U.S. women within the positive tamoxifen risk–benefit categories of Gail et al. account for few breast cancers and are very few in number. The letter bases this view on percentages involving women 50–69 years old and on risk–benefit benefit cutoff figures from Table 10 of Gail et al. (3), although Table 12 in the same article would have been more relevant for comparisons with NHS “healthy volunteers.” On the other hand, let us consider only the Breast Cancer Prevention Trial (BCPT) women who were less than 50 years old—approximately 5300 women (approximately 40% of the 13 388 total). Tables 10 and 11 in the article by Gail et al. (3) indicate that all of these women were in positive risk–benefit categories. A rough extrapolation suggests that there are from 2 to 4 million such tamoxifen-eligible women in the United States [relevant data: 23% of eligible screened women were accrued to BCPT (6); 35–49 years old = 56% of BCPT women <60 years old (6); and 9 million 35- to 59-year-old U.S. women fit BCPT eligibility (McCaskill-Stevens W, Ford LG: personal communication)]. Any counting based on this line of reasoning would result in at least hundreds of thousands of U.S. women with positive tamoxifen risk–benefit ratios. Tamoxifen use in the BCPT was associated with 28 fewer breast cancers (versus placebo) per 1000 women (<50 years old) in 5 years (2). Therefore, the numbers of breast cancers in U.S. women potentially prevented by tamoxifen in 5 years run from 2800 (if there are only 100 000 eligible women) to 56 000 (if 2 million women are eligible).

Obviously, the two lines of reasoning outlined above show a disconnect between the indications of the BCPT and the NHS. This disconnection is one of many fascinating issues raised by our commentary, and we look forward to hearing more from both sides.

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In their critique of the excellent commentary by Lippman and Brown (1), Rockhill et al. challenge statements that I made in a recent commentary that related to the National Surgical Adjuvant Breast and Bowel Project Breast Cancer Prevention Trial (BCPPT P-1) (2). In my remarks, I speculated on the consequences of administering tamoxifen to a larger population of eligible women than that which comprised the P-1 study, “even though the vast majority of them would never develop breast cancer and even though not all tumors would be prevented in the women who would have had a tumor” (2). I related the average annual rate (6.76) of occurrence of invasive breast cancer in each 1000 participants in the placebo group of the P-1 study (3) to the approximately 29 million women in the United States comprising 21% of the adult female population who had been estimated by the National Cancer Institute to be potentially eligible for the P-1 trial (4). On the basis of that association, it was estimated that, during a 5-year period, almost 1 million of the 29 million, i.e., about 200,000 women per year, would have the potential for being diagnosed with invasive breast cancer. Because the rate was reduced to 3.43 per 1000 women per year in the tamoxifen group of the P-1 study, it was estimated that almost 500,000 invasive breast cancers might be prevented in the expanded population over a 5-year period.

The results obtained by extrapolating the findings of the P-1 study to a larger group of similar women demonstrate the potential impact that the more widespread use of tamoxifen could have in lessening the extent of the breast cancer problem. Despite this, in their letter, Rockhill et al. imply that my argument is based on “unrealistic estimates of numbers of cases of breast cancer prevented.” The reason for their skepticism is difficult to comprehend. It seems that Rockhill et al. have based much of their concern on the fact that, because only about 180,000 new cases of invasive breast cancer are being detected in the United States each year, it would be unrealistic to anticipate that “1.4 million cases of breast cancer might be expected during the course of 5 years,” an erroneous estimate that they made.

Rockhill et al. also fail to realize that the number of cases of invasive breast cancer that are being diagnosed each year represents only a fraction of the number of women who are actually at risk for the disease because many of them have undetected molecular-biologic or phenotypic changes in breast cells that put them at increased risk for developing a detectable invasive breast cancer at some future time. It was that concept that led us to conduct the P-1 study.

Although essentially correct, the statement by Rockhill et al. that “Fisher even cited a possible reduction of 1 million cases of breast cancer in 5 years, if 2 million cases were to occur among women eligible for the drug” is misleading because it was taken out of context. In my commentary (2), I presented several hypothetical circumstances to emphasize that the magnitude of benefits observed in the P-1 study was related to the level of breast cancer risk in the women being evaluated. I stated, “If, for example, the 5-year predicted risk in all of the women comprising the 29 million were ≥5.01%, it would be estimated that almost 2 million invasive cancers would have occurred in the placebo group and 650,000 in the tamoxifen group during a 5-year period. Thus, approximately 1.2 million invasive cancers might have been prevented” (2). I then asserted, “if the 5-year predicted risk in all 29 million women were ≤2.0%, then approximately 500,000 tumors might have been prevented” (2). I emphasized further that in none of the circumstances did I imply that all 29 million women should receive tamoxifen.

While the article by Gail et al. (5) may be viewed as a tour de force, using it to diminish the importance of the P-1 trial, as Rockhill et al. have done, is highly inappropriate. Not only have Gail et al. and other investigators (6) provided enough caveats to indicate that many of their “methods are subject to various uncertainties” (5), but also I have emphasized (2) that to estimate the net benefit from tamoxifen by merely subtracting the number of adverse events from the number of cancers prevented and then using the resulting value to formulate conclusions about whether a drug should be given is too simplistic. Such an approach leads to the erroneous assumption that all events are equivalent relative to their significance and, consequently, engenders doubt about the use of tamoxifen, even where appropriate, as a breast cancer preventive agent.

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REFERENCES


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