Re: Estimation of Tamoxifen’s Efficacy for Preventing the Formation and Growth of Breast Tumors

The recent report by Radmacher and Simon (1) addressed the issue of whether the effect of tamoxifen observed in the National Surgical Adjuvant Breast and Bowel Project’s Breast Cancer Prevention Trial (BCPT) (2) was “mainly due to prevention of newly forming tumors or to treatment of occult disease.” On the basis of analyses in various tumor growth models, those authors (1) concluded that the reduced tumor incidence in the tamoxifen-treated group was probably due to both effects.

By contrast, our recent data (3) obtained with the use of a transgenic mouse model of spontaneous development of HER2/neu-positive, estrogen-independent tumors suggest that the protective effect observed in the BCPT is due only to treatment of occult disease. Indeed, in our animal model, early treatment with tamoxifen inhibited the formation of terminal buds in the mammary gland and clearly prevented spontaneous tumors. In contrast, late treatment—when subclinical tumors were already present—had no effect, as expected for the treatment of estrogen-independent tumors.

In the clinical trial, protection only from estrogen receptor-positive tumors was observed, consistent with the dependence on receptor expression of the therapeutic effect of tamoxifen—if tamoxifen acted to prevent new tumors by reducing the number of normal breast epithelial cells at risk of transformation, then both estrogen receptor-positive and estrogen receptor-negative tumors should have been prevented. Moreover, the reduced incidence of breast cancer associated with tamoxifen was not more pronounced in premenopausal women, in whom tamoxifen is likely to inhibit the hormones that govern homeostasis of the normal epithelial cells during the different phases of the menstrual cycle.

Therefore, we think that the protective effect observed in the BCPT is due mainly to the treatment of occult disease. However, it might well be that a longer follow-up period in the BCPT will reveal a reduced incidence of estrogen receptor-negative tumors after long-term treatment with tamoxifen, indicating the prevention of newly formed tumors.

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RESPONSE

Ménard et al. report that, in their mouse model, early treatment (before spontaneous tumor formation) with tamoxifen prevented both estrogen receptor-negative (ER−) and ER-positive (ER+) tumor formation, while late treatment was effective only against ER+ tumors. Since only ER+ tumor incidence was reduced in the National Surgical Adjuvant Breast and Bowel Project’s BCPT (1), they conclude that the protective effect of tamoxifen in the trial was limited to treatment of occult disease. We disagree with this conclusion, since the small number of ER− tumors detected during the trial and the potential opposing effects of tamoxifen on occult and new ER− tumors made it difficult to detect a reduction in ER− tumor incidence, even if one existed.

Although no reduction—and, in fact, a slight increase—in the incidence of ER− tumors were observed in the treatment arm of the BCPT (1), some evidence of time-dependent effects exists. As shown in Table 1, an excess of ER− tumors (i.e., 22) was detected in the tamoxifen group during the first 2 years of the trial when compared with the number that occurred in the placebo group (i.e., nine). However, in each year after the second year, the number of ER− tumors detected in the tamoxifen group was less than the number detected in the placebo group. As indicated by the various breast tumor growth models that we considered in our analysis of the BCPT (2), we would expect that the vast majority of tumors detected within the first 2 years of study entry were occult at entry. The increase in incidence of ER− tumors in the tamoxifen group during the first 2 years of the trial, if indeed it is not just a statistical fluctuation, is likely due to some effect on occult disease. This observation is consistent with the finding by Ménard et al. (3) of an acceleration in estrogen-independent tumor development in mice treated with tamoxifen after the appearance of subclinical disease. The suggested decrease in ER− tumor incidence in later years of the BCPT (as new tumors become more prevalent) may be indicative of a pre-
The preventive effect of tamoxifen on new ER− tumor formation.

Using the likelihood model that we developed previously (2) on the data from Table 1, we estimated tamoxifen’s efficacy for treating occult ER− tumors (bTr) and preventing new ER− tumor formation (bPr) during the BCPT. The parameters are continuous with an upper limit of 1.0, where 1.0 indicates that 100% of tumors are effectively eliminated or prevented from forming, 0 indicates that tamoxifen has no effect, and a negative value indicates that tamoxifen leads to an increase in tumor incidence. The maximum likelihood estimates of bTr were negative for all four tumor growth models, ranging from –1.40 to –0.53 [strikingly different than the estimates from the ER+ analysis, which ranged from 0.70 to 0.80 (2)]. The estimates of bPr ranged from 0.26 to 1.00. These estimates of the preventive effect for ER− tumors are of the same sign and average magnitude as the estimates from the ER+ analysis, which ranged from 0.63 to 0.67 (2). Although the confidence limits were broad because of the small number of ER− tumor events, the estimates of bTr are consistent with the hypothesis that overall ER− tumor incidence is increased in the tamoxifen group as a result of an acceleration of occult ER− tumor development, while prevention of new ER− tumors occurred at a similar rate as for ER+ tumors.

In conclusion, rejecting our inference (that both a treatment and preventive effect reduced ER+ tumor incidence in the BCPT) based on the lack of a similar reduction for ER− tumors is inappropriate for at least two reasons. First, only total (occult plus new) tumor incidence is observable. Thus, an acceleration of occult ER− disease may have masked a preventive effect on new ER− tumor formation in the BCPT. Second, many fewer ER− than ER+ tumors were detected during the BCPT and, therefore, the power to detect a preventive effect on ER− tumors was greatly diminished.

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REFERENCES

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Table 1. Estrogen receptor-negative (ER−) tumor incidence data from the Breast Cancer Prevention Trial*

<table>
<thead>
<tr>
<th>Year</th>
<th>Placebo group</th>
<th>Tamoxifen group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Person-years at risk</td>
<td>ER− tumors</td>
</tr>
<tr>
<td>1</td>
<td>6359</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>5626</td>
<td>7</td>
</tr>
<tr>
<td>3</td>
<td>5020</td>
<td>9</td>
</tr>
<tr>
<td>4</td>
<td>4598</td>
<td>7</td>
</tr>
<tr>
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<td>4</td>
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<tr>
<td>6</td>
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</tr>
<tr>
<td>Total</td>
<td>25 878</td>
<td>31</td>
</tr>
</tbody>
</table>

*Data were provided by the National Surgical Adjuvant Breast and Bowel Project.