Tamoxifen has been administered to thousands of women during the last 30 years. Initially, it was used for treatment of metastatic breast cancer, next for adjuvant treatment of breast cancer, and most recently for reduction in the incidence of breast cancer in high-risk women. Tamoxifen is one of the first molecularly targeted therapies to be successful in improving survival in a large number of patients with a common cancer. It is thought that tamoxifen functions as an antiestrogen by structurally altering the estrogen receptor (ER), which thereby disrupts the ER–estradiol complex (1). An overview of randomized trials of adjuvant hormonal therapy with tamoxifen included information on 37,000 women, of whom 18,000 were ER positive and 12,000 had unknown ER status (2). This overview showed that the 10-year survival of women who had ER-positive tumors was increased substantially by tamoxifen treatment. The absolute increase in survival was 10.9% for women with lymph node-positive disease and 5.6% for women with lymph node-negative disease. The mortality reduction had a statistically significant trend, with a greater effect with longer treatment. The proportional mortality reductions after 1, 2, and 5 years of treatment were 12%, 17%, and 26%, respectively. Updated results presented at the most recent Early Breast Cancer Trialists’ Collaborative Group meeting in Oxford, U.K., in September 2000 revealed similar results. Tamoxifen use clearly improved the survival of women with ER-positive breast cancer or breast cancer of unknown ER status, with 17% and 34% proportional reductions in mortality, respectively. There were no decreases or increases in mortality in women with ER-negative breast cancer who were treated with tamoxifen. The public health implications of this mortality reduction in women treated with tamoxifen are substantial.

One of the other reasons for administering tamoxifen is for the reduction of breast cancer in the contralateral breast. In this issue of the Journal, Li et al. (3) report that they did not find a statistically significant reduction in contralateral breast cancer in women treated with adjuvant tamoxifen, with a hazard ratio of 0.9 (95% confidence interval [CI] = 0.7 to 1.2). This negative finding seriously calls into question the generalizability of the results of the subset analyses presented by Li et al. The overview data demonstrated a 30% reduction in contralateral breast cancer in women with ER-positive breast cancer that increases with longer duration of treatment (Table 1) (2). Rutqvist et al. (4) also found a 40% decrease in contralateral breast cancer in patients treated with tamoxifen. Mamounas et al. (5) have reported the results of nine National Surgical Adjuvant Breast and Bowel Project (NSABP) studies and found a 40% decrease in contralateral breast cancer in patients who received tamoxifen compared with those who did not. That analysis was based on a model that assumed that the effect of tamoxifen was the same in patients with ER-negative or ER-positive tumors. NSABP B-14, in which patients with ER-positive tumors were treated, found a statistically significant 37% reduction in contralateral breast cancer (6). Finally, the same group who report the results in this issue of the Journal (3) published a case–control study that found a 50% decrease in contralateral breast cancer in women treated with tamoxifen (7).

Therefore, the results presented in the report by Li et al. (3) in this issue are inconsistent with other data in the literature obtained by an overview, by randomized comparisons, or by a population-based case–control study. Since information on tamoxifen duration is not captured in the report by Li et al., it is possible that many of the patients included in that analyses took tamoxifen for less than 1 year. As shown in Table 1, treatment with tamoxifen for 1 year or less was not associated with a statistically significant decrease in contralateral breast cancer in the overview study (2) and in the study by Cook et al. (7).

Li et al. (3) performed a subset analysis in women who developed contralateral breast cancer and conclude that tamoxifen appears to decrease the risk of ER-positive contralateral breast cancer and to increase the risk of ER-negative contralateral breast cancer (3). Their conclusion is based on a retrospective cohort study of a select subset of women: women 50 years old or older, who had or had not received tamoxifen only as adjuvant treatment and no chemotherapy. A population-based cancer registry was used to identify 8981 women who met these criteria. By reviewing abstracted data, Li et al. have documented tamoxifen use in 94% of patients classified as tamoxifen users. This percentage may seem reasonable, but a 6% treatment misclassification error may be substantial, considering that conclusions are being based on a very small number of contralateral breast cancer cases with ER-negative tumors. Li et al. did not provide a definition of ER negativity, which is a problem because the analysis of ER status by immunohistochemistry (IHC) has not been standardized and the definition of positivity and negativity varies by laboratory (8). It has been reported that tamoxifen treatment of patients with as few as 1% ER-positive cells as measured by IHC was associated with an increase in disease-free survival (9). This result suggests that tumors classified as ER negative by some groups may actually be hormone sensitive.

In the study by Li et al. (3), a total of 189 women with contralateral breast cancer were identified, of whom 57 (30%) were not included in the analyses because their ER status was unknown or had been determined by the ligand-binding assay. The latter exclusion is appropriate, since tamoxifen use will result in a false-negative ER result in the ligand-binding assay

Affiliation of author: Medicine Branch, Center for Cancer Research, National Cancer Institute, Bethesda, MD.

Correspondence to: Sandra M. Swain, M.D., National Institutes of Health, 10 Center Dr., Bldg. 10, Rm. 12N226, MSC 1906, Bethesda, MD 20892–1906 (e-mail: Swains@mail.nih.gov).
The analysis of the receptor status of the contralateral breast cancer in women whose ER status in the contralateral breast cancer was measured by IHC left a total of 64 women with contralateral breast cancer in the tamoxifen users and 68 in the nonusers. Li et al. (3) found 47 women with ER-positive contralateral breast cancers in the tamoxifen user group and 65 women with ER-positive contralateral breast cancers in the nonuser group, which had a statistically nonsignificant hazard ratio for tamoxifen users compared with nonusers of tamoxifen of 0.8 (95% CI = 0.5 to 1.1). The conclusion that there is an increase in ER-negative contralateral breast cancer was based on the results obtained on only 20 patients, 17 users of tamoxifen and three nonusers. The hazard ratio based on these numbers was 4.9 (95% CI = 1.4 to 17.4). The small number of events with a corresponding wide CI in a retrospective study does not provide clear evidence that the increased risk of ER-negative contralateral breast cancer is associated with tamoxifen use. Another study that considered the ER status of contralateral breast cancers in women treated with tamoxifen (11) found that seven (47%) of 15 tamoxifen-treated patients had an ER-negative contralateral breast cancer versus three (12%) of 25 control subjects. Unfortunately, since the numbers are small and the ER status was known for only 53% of the patients, that study also makes a definitive conclusion impossible.

### Table 1. Risk ratio of contralateral breast cancer in tamoxifen-treated patients versus patients not treated with tamoxifen

<table>
<thead>
<tr>
<th>Tamoxifen duration</th>
<th>Risk ratio (tamoxifen/no tamoxifen)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overview 1998 (2)</td>
<td>1 y</td>
<td>0.87</td>
</tr>
<tr>
<td></td>
<td>2 y</td>
<td>0.74</td>
</tr>
<tr>
<td></td>
<td>5 y</td>
<td>0.53</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>0.70</td>
</tr>
<tr>
<td>Rutqvist et al. (4)</td>
<td>2 or 5 y</td>
<td>0.60</td>
</tr>
<tr>
<td>Mamounas et al. (5)</td>
<td>&gt;5 y</td>
<td>0.60</td>
</tr>
<tr>
<td>NSABP B-14 (6)</td>
<td>5 or 10 y</td>
<td>0.63</td>
</tr>
<tr>
<td>Cook et al. (7)</td>
<td>All</td>
<td>0.50†</td>
</tr>
<tr>
<td></td>
<td>&lt;12 mo</td>
<td>0.70</td>
</tr>
<tr>
<td></td>
<td>≥13 mo</td>
<td>0.40</td>
</tr>
<tr>
<td>Li et al. (3)</td>
<td>Not determined</td>
<td>0.90</td>
</tr>
</tbody>
</table>

*CI = confidence interval; NSABP = National Surgical Adjuvant Breast and Bowel Project.
†Matched odds ratio.

No biologic data support the hypothesis that tamoxifen promotes ER-negative breast cancer. In fact, a comprehensive review of ER expression in breast cancer (12) concludes that ER expression is a stable phenotype. That is, there is no phenotypic drift, even in metastatic disease, after treatment with tamoxifen. However, there may be a decreased expression of the ER. It is known that breast cancer is heterogeneous and contains both ER-negative and ER-positive cells, which most likely have different origins, as has been recently suggested by gene-profiling studies of breast tumors (13). A more plausible scenario is that, when breast cancer is treated with tamoxifen, the ER-positive cells respond by decreasing proliferation and the ER-negative cells may continue to grow by selective pressure.

Two studies, the NSABP P-1 study (14) and the Multiple Outcomes of Raloxifene Evaluation trials (15), support the concept that tamoxifen has an effect only in ER-positive breast cancers. These two prospective trials examined the risk of developing breast cancer after treatment with a selective ER modulator, and neither produced data that supported an increase in ER-negative breast cancer after such treatment. The NSABP P-1 study (14) reported a statistically significant decrease of 69% in the incidence of ER-positive cancers in high-risk women treated with tamoxifen compared with women treated with placebo but no difference in ER-negative cancers (Table 2). The Multiple Outcomes of Raloxifene Evaluation trial (15) found that raloxifene decreased the risk of ER-positive breast cancer by 90% but had no statistically significant effect on the risk of ER-negative breast cancer, although the findings were based on small numbers of patients.

Reviewing these data collectively, it is clear that tamoxifen is associated with a substantial decrease in the incidence of contralateral breast cancer in women with ER-positive disease. Also, in the two studies that showed an effect of tamoxifen in high-risk women only (14,15), the incidence of ER-positive cancers decreased, with no effect on ER-negative cancers. If, as Li et al. (3) suggest, more ER-negative contralateral breast cancers occur in women treated with tamoxifen, one would have expected a decrease in survival in women treated with tamoxifen. This is not the case. In fact, the opposite has been found, as discussed above.

In summary, the study by Li et al. (3) has noteworthy limitations. It is a retrospective analysis, assessing a treatment effect when treatment was not randomly assigned. It is a subset analysis that excludes substantial numbers of cases within the subset and includes only a small number of events upon which to draw conclusions. Consequently, the study does not provide reliable evidence that is sufficient to make any conclusions regarding the ER status of contralateral breast cancer in women treated with tamoxifen. However, it does point out correctly that the determination of ER status of contralateral breast cancers is important, and it is the first study in which attempts were made to evaluate this issue in a large number of patients.

### References


