Estrogen Receptor Status of Primary Breast Cancer Is Predictive of Estrogen Receptor Status of Contralateral Breast Cancer

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Background: Tamoxifen reduces the risk for contralateral breast cancer by approximately 30%–50%, with benefits probably limited to women with estrogen receptor (ER)-positive primary disease. In a retrospective analysis of data from National Surgical and Adjuvant Breast and Bowel Project trials B-18, B-22, and B-25, we determined whether the ER status of primary breast cancer predicts the ER status of a subsequent contralateral breast cancer and whether tamoxifen treatment affects this relationship. In these trials, tamoxifen at 20 mg/day had been administered only to women aged 50 years or older, rather than to those determined by the ER status of their primary tumor, allowing an assessment of the treatment’s effects in ER-negative disease. Methods: Among the 5513 eligible patients, 176 patients developed a contralateral breast cancer. The ER status of the primary and contralateral tumor was determined and cross-classified for women who did not receive tamoxifen (i.e., those aged 49 years or younger) and for women who did (i.e., those aged 50 years or older). ER data were available for 110 evaluable invasive contralateral breast cancers. Results: Among patients who did not receive tamoxifen (n = 62), 89% with an ER-positive primary cancer had an ER-positive contralateral breast cancer and 70% with an ER-negative primary cancer had an ER-negative contralateral breast cancer (odds ratio for the association between primary and contralateral ER status = 14.8, 95% confidence interval = 3.8 to 74.3; P < .001). Among patients who received tamoxifen (n = 48), 56% with an ER-positive primary cancer had an ER-positive contralateral breast cancer and 78% with an ER-negative primary cancer had an ER-negative contralateral breast cancer (odds ratio = 3.4, 95% confidence interval = 0.53 to 39.2; P = .25). Conclusion: The ER status of the primary breast cancer was associated with that of the contralateral breast for patients not receiving tamoxifen. Patients with an ER-positive primary cancer who received tamoxifen had a lower concordance rate with fewer ER-positive contralateral breast cancers, which may be a result of tamoxifen treatment. [J Natl Cancer Inst 2004;96:516–23]

Women with breast cancer have a risk of developing contralateral disease that is higher than the risk of developing a first breast cancer in the general population (1). The National Surgical Adjuvant Breast and Bowel Project (NSABP) has recently reported long-term follow-up from two large randomized trials (NSABP B-04 and NSABP B-06), in which the occurrence of contralateral breast cancer as a first event among women with operable breast cancer ranged from 6% to 8.9%, with 50% to 60% of the cases occurring more than 5 years after treatment of the primary tumor (2,3). Risk factors for contralateral breast cancer include lobular histology (invasive and in situ disease) (4–6), family history (5,6), and age (5,6). Although long-term follow-up from two large randomized trials reveals no increase in the risk of contralateral breast cancer after radiation therapy (3,7), a recent report that was based on data from the Surveillance, Epidemiology, and End Results program suggests that radiation is associated with a very small increase in risk (8). The effect of contralateral breast cancer on survival has been evaluated in several retrospective studies. The length of time between treatment of the primary tumor and development of contralateral breast cancer appeared to influence survival in some studies, with a shorter interval associated with poorer survival (4,6,9).

Adjuvant tamoxifen reduces the risk of contralateral breast cancer by 30%–50% for women with breast cancer (10–13). NSABP B14 demonstrated the survival benefits associated with 5 years of tamoxifen therapy in more than 2800 women with lymph node-negative, estrogen receptor (ER)-positive breast cancer, and a 37% decrease in the risk of contralateral breast cancer after 10 years of follow-up (10). These data provided the rationale for the evaluation of tamoxifen for the prevention of breast cancer in healthy women. In the NSABP P-1 study, 13 388 women at high risk for developing breast cancer were randomly assigned to treatment either with tamoxifen at 20 mg/day or with placebo for 5 years (14). Tamoxifen significantly reduced the risk of invasive breast cancer by 49% and the risk of ER-positive breast cancer by 69%. There was no effect on the risk for ER-negative disease. Several other trials in healthy women have been conducted (15–18), and a combined analysis of all the trials reveals that women treated with tamoxifen have a 30%–40% reduced risk of breast cancer (19). Although the incidence of ER-positive tumors was statistically significantly reduced, the incidence of ER-negative breast cancer was not affected (19). These findings are consistent with the results from randomized trials conducted in women with breast cancer, which have not shown a decrease in contralateral breast cancer for women with ER-negative disease treated with tamoxifen (20). These data thus suggest that tamoxifen either interferes directly with tumor initiation and promotion or has a treatment effect on undetectable occult disease. These effects appear to be...
limited to estrogen-dependent tumors, which is consistent with the mechanism of action of tamoxifen.

Whether contralateral breast cancer represents a second primary versus recurrent or metastatic disease clearly has implications for treatment. For example, if contralateral breast cancer represents a second, biologically distinct primary cancer, treatment with tamoxifen may be beneficial for women with an ER-negative primary cancer who are at risk for developing contralateral disease. Attempts to describe the natural history of breast cancer and to determine the relationship between primary and contralateral disease have included analyzing concordance among prognostic factors, such as hormone receptor status. Concordance between synchronous and metachronous primary and secondary breast tumors was found in the majority of cases in one early study (21). Coradini et al. (22) reported that the correlation between ER levels is higher between a primary tumor and a synchronous contralateral breast cancer than between a primary tumor and a metachronous contralateral breast cancer, but the correlation was still present with metachronous cancers. In addition, adjuvant hormonal treatment, compared with no hormonal treatment, was associated with a reduction in quantitative ER levels of the contralateral breast cancer, with this difference decreasing with time (22).

This study was undertaken to determine whether the ER status of a primary invasive breast tumor is predictive of the ER status of a subsequent contralateral tumor and whether tamoxifen treatment affects this association. This was a retrospective analysis of the concordance rate for hormone receptor status between primary and contralateral breast cancer in a cohort of women with operable breast cancer who participated in one of three recent NSABP clinical trials. We hypothesized that the ER status of the primary tumor would predict the ER status of the contralateral breast cancer in women who did not receive tamoxifen but that this relationship would be attenuated in women who received tamoxifen. Data from NSABP trials B-18, B-22, and B-25 were used because all three are contemporary trials in which the use of tamoxifen was not predicated on hormone receptor status (23–26). By design, tamoxifen was given to all women aged 50 years or older and to no women aged 49 years or younger. Two patients who were younger than age 50 years at surgery received tamoxifen as exceptions to the initial protocol and are included in the “tamoxifen” group in the current analysis. One additional patient who developed an invasive contralateral breast cancer was aged 51 years at the time of randomization and refused tamoxifen treatment. This patient is included in the “no tamoxifen” group in the current analysis. Thus, the current analysis was conducted by treatment received, rather than by intent-to-treat.

ER Analysis

Determination of ER results was conducted at individual study sites and was defined according to the reporting institution’s laboratory guidelines. ER status was determined by several methods. Immunohistochemistry was used for 63% of the cases, biochemical analysis for 24% of the cases, enzyme-linked immunosorbent assay or enzyme immunoassay for 4% of the cases, and an unknown method for 9% of the cases. Dr. Soon Paik (NSABP) performed ER analysis by immunohistochemistry on the nine cases for which he received tumor blocks. Data from two of these cases were included in the analysis, and data from the other seven were excluded because the patients had noninvasive contralateral disease.

Trials

Complete details on the design and purpose of the NSABP studies from which the current patient cohort was derived have been described elsewhere and are briefly summarized below (23–26). At the time of this analysis (summary file cut-off date

Subjects and Methods

Design

A retrospective analysis of the ER status of primary and subsequent contralateral invasive breast cancers in NSABP trials B-18, B-22, and B-25 was conducted. Noninvasive contralateral breast cancers were excluded because ER analyses were not routinely performed on these cases. Documentation of a contralateral breast cancer in the protocols was required. This definition included any contralateral breast cancer noted as a first event. The primary outcome of this study was the ER status concordance rate for primary and contralateral breast cancer, stratified by use of tamoxifen. The receptor status of the primary tumor and the subsequent contralateral breast cancer were determined and cross-classified to investigate the degree to which the former is predictive of the latter. The analysis was done separately for patients who did and did not receive tamoxifen. Additional analyses included an assessment of the concordance between the histology of the primary tumor and subsequent contralateral breast cancer. Duration of survival following diagnosis of contralateral breast cancer was also compared between patients with ER-negative and ER-positive contralateral breast cancers. Histology was determined from pathology reports submitted by the study sites when the contralateral events were reported, and survival was determined from the original follow-up of all patients on these protocols.

Patient Identification

Patients from NSABP trials B-18, B-22, and B-25 who were eligible for follow-up and who were diagnosed with a subsequent contralateral breast cancer as a first-event were identified by querying the databases from the three studies. The ER status of the primary tumor of each patient was determined from data submitted after initial enrollment to the respective NSABP trial. Individual charts were reviewed at the NSABP Biostatistical Center to obtain the ER status of the contralateral breast cancer. If the information had not been submitted as part of the documentation at the time the contralateral breast cancer was reported, written requests for the ER reports were mailed to the individual study sites, and follow-up phone calls were made if necessary. If there was no documentation, then paraffin-embedded tumor blocks were requested, sectioned, and analyzed. Tumor blocks were obtained in nine cases.

Compliance with the assigned hormonal treatment was evaluated during chart review. In each trial, tamoxifen was to be given to patients aged 50 years or older, but not to patients aged 49 years or younger. Two patients who were younger than age 50 years at surgery received tamoxifen as exceptions to the initial protocol and are included in the “tamoxifen” group in the current analysis. One additional patient who developed an invasive contralateral breast cancer was aged 51 years at the time of randomization and refused tamoxifen treatment. This patient is included in the “no tamoxifen” group in the current analysis. Thus, the current analysis was conducted by treatment received, rather than by intent-to-treat.
June 30, 2001), the median follow-up in each trial was 99.8, 108.6, and 82.9 months in trials B-18, B-22, and B-25, respectively. All patients were required to have a mammogram before study entry. All protocols were approved by institutional review boards, and all patients provided written informed consent.

NSABP B-18 enrolled 1523 patients with primary, palpable, operable breast cancer confined to the breast or axilla (T1, 2, 3, N0, 1, M0) from October 1988 through April 1993 to determine whether four cycles of AC (doxorubicin and cyclophosphamide at 60 and 600 mg/m², respectively, every 21 days) given preoperatively improves overall survival and disease-free survival when compared with the same chemotherapy regimen given postoperatively (23). Patients were randomly assigned to surgery followed by adjuvant AC or to preoperative AC followed by surgery. All patients who underwent breast-conserving surgery received postoperative radiation, and patients aged 50 years or older received tamoxifen at 20 mg/day for 5 years, beginning on the day after the last dose of chemotherapy. Women aged 49 years or younger did not receive tamoxifen, even if the primary cancer was ER-positive. Through 9 years of follow-up, there were no differences in disease-free survival, distant-disease-free survival, or overall survival between groups (27). For the purposes of this analysis, patients randomly assigned to preoperative therapy were excluded because of the lack of primary tumor hormone receptor assays for a large number of patients, which is related to the diagnosis being made from a fine-needle aspirate. Thus, there were 751 patients from this trial included in the current analysis.

NSABP B-22 enrolled 2305 patients with lymph node-positive, primary operable breast cancer from July 1989 through May 1991 to assess the effect of dose-intensive and higher-dose cyclophosphamide on disease-free and overall survival in this patient population. The 2254 patients with complete follow-up are included in the current analysis (25). Patients were randomly assigned to one of three adjuvant chemotherapy groups: group 1, standard AC (doxorubicin at 60 mg/m² and cyclophosphamide at 600 mg/m² every 21 days for four cycles); group 2, intensified AC (doxorubicin at 60 mg/m² for four cycles with cyclophosphamide at 1200 mg/m² for two cycles), and group 3, intensified, increased-dose AC (doxorubicin at 60 mg/m² and cyclophosphamide at 1200 mg/m² for four cycles). All patients who underwent breast-conserving surgery received postoperative radiation, and all patients aged 50 years or older received tamoxifen at 20 mg/day for 5 years, beginning on day 1 of the first cycle of chemotherapy. Patients aged 49 years or younger did not receive tamoxifen, regardless of ER status. At 5 years, there were no differences in disease-free or overall survival between group 1 and either group 2 or group 3.

NSABP B-25 enrolled 2548 patients with lymph node-positive, primary operable breast cancer between April 1992 and February 1994 to assess whether further chemotherapy dose intensification and dose increases improve disease-free and overall survival in this patient population (26). Of these patients, 2508 were eligible with complete follow-up and are included in the current analysis. Patients were randomly assigned to one of three adjuvant chemotherapy groups, with cycles repeated every 21 days: group 1, doxorubicin at 60 mg/m² and cyclophosphamide at 1200 mg/m² for four cycles; group 2, doxorubicin at 60 mg/m² for four cycles and cyclophosphamide at 2400 mg/m² for two cycles; and group 3, doxorubicin at 60 mg/m² and cyclophosphamide at 2400 mg/m² for four cycles. All patients received granulocyte colony-stimulating factor at 5 μg/kg/day, beginning on day 2 of chemotherapy until a granulocyte count of more than 10 000/mm³ was reached after day 7. All patients who underwent breast-conserving surgery received postoperative radiation, and all patients aged 50 years or older received tamoxifen at 20 mg/day for 5 years, beginning on day 1 of the first cycle of chemotherapy. Patients aged 49 years or younger did not receive tamoxifen, regardless of ER status. At 5 years, there were no statistically significant differences in disease-free, distant-disease-free, or overall survival among the three groups.

Statistical Methods

To examine the association between primary tumor and contralateral breast cancer ER status, data were arranged in separate 2 × 2 tables for patients aged 49 years or younger at study entry (i.e., those patients who did not receive tamoxifen) and for patients aged 50 years or older at study entry (i.e., those patients who received tamoxifen). Each 2 × 2 table was stratified by protocol (B-18, B-22, or B-25) to take account of protocol-related differences in treatment, patient population, and other factors. Zelen’s test was used to assess the homogeneity of odds ratios (ORs) (28). After homogeneity was assessed and accepted, a Mantel–Haenszel test (with the P value generated using permutations) was used to test the null hypothesis that the common OR was equal to 1; meaning that, primary and contralateral ER status were independent (29,30). The association between primary and contralateral tumor histology was also assessed using a Mantel–Haenszel test. Survival curves were estimated using the Kaplan–Meier method (31), and cumulative incidence was calculated as in Kalbfleisch and Prentice (32). Differences between survival curves were assessed using log-rank tests (32). All reported P values are two-sided.

RESULTS

Contralateral Breast Cancers

A total of 5513 patients from studies B-18, B-22, and B-25 were eligible for analysis in this study. Within this group, a total of 176 contralateral breast cancers were diagnosed as a first event with a median follow-up from time on study to contralateral breast cancer of 53.7 months (range = 2.8–123.7 months) (Table 1). The overall cumulative incidence of contralateral breast cancer (invasive or in situ) at 8 years was 3.3%, with a range of 1.7%–3.7% in specific study arms.

There were 110 evaluable cases of invasive contralateral breast cancer (63%). Sixty-six cases of contralateral breast cancer were excluded from the analysis because of unknown ER status of the primary tumor (n = 4), the contralateral tumor (n = 21) or both (n = 3) or for noninvasive disease (n = 38). At the time the NSABP studies were conducted, ER testing was not done routinely on samples from patients with noninvasive disease. Missing data were evenly distributed among the three protocols. Table 2 compares the demographic characteristics of the entire eligible group to those of patients with invasive contralateral breast cancer who were eligible for the analysis, and to those of patients with invasive contralateral breast cancer for whom ER data were missing. The study cohort did not differ statistically significantly from the general population of eligible patients with respect to any characteristics. With the exception
Table 1. Incidence of contralateral breast cancer (invasive or in situ) by study arm for patients enrolled in National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18, B-22, and B-25 randomized trials*

<table>
<thead>
<tr>
<th>Trial and treatment regimen</th>
<th>No. of eligible patients</th>
<th>Total No. of patients with CBC</th>
<th>Cumulative incidence at 8 y, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-18, adjuvant chemotherapy</td>
<td>751</td>
<td>33</td>
<td>3.5</td>
</tr>
<tr>
<td>B-22, A 60 × 4 C 600 × 4</td>
<td>755</td>
<td>32</td>
<td>3.2</td>
</tr>
<tr>
<td>B-22, A 60 × 4 C 1200 × 2</td>
<td>742</td>
<td>29</td>
<td>3.7</td>
</tr>
<tr>
<td>B-25, A 60 × 4 C 1200 × 4</td>
<td>834</td>
<td>21</td>
<td>2.5</td>
</tr>
<tr>
<td>B-25, A 60 × 4 C 2400 × 2</td>
<td>840</td>
<td>14</td>
<td>1.7</td>
</tr>
<tr>
<td>Total</td>
<td>5513</td>
<td>176</td>
<td>3.3</td>
</tr>
</tbody>
</table>

*For B-18, only patients enrolled in the adjuvant chemotherapy arm were eligible for this analysis. For B-22 and B-25, treatment arms are identified by the respective Adriamycin (A) and cyclophosphamide (C) regimen administered as drug, dose in mg/m², and number of cycles (× No.). CBC = contralateral breast cancer.

Table 2. Demographics of patients enrolled in National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18, B-22, and B-25 randomized trials at study entry*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Eligible patients, N = 5513</th>
<th>Patients with invasive CBC and known ER status, N = 110</th>
<th>Patients with invasive CBC but missing ER data, N = 28</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range), y</td>
<td>48 (21–75)</td>
<td>47 (26–75)</td>
<td>46.5 (32–70)</td>
</tr>
<tr>
<td>Median time from randomization to CBC (range), y</td>
<td>N/A</td>
<td>4.66 (0.26 to 10.3)</td>
<td>4.16 (0.23 to 8.3)</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>85.5%</td>
<td>86%</td>
<td>89%</td>
</tr>
<tr>
<td>African American</td>
<td>8.8%</td>
<td>9%</td>
<td>11%</td>
</tr>
<tr>
<td>Other</td>
<td>5%</td>
<td>4%</td>
<td>0</td>
</tr>
<tr>
<td>Unknown</td>
<td>0.6%</td>
<td>1%</td>
<td>0</td>
</tr>
<tr>
<td>Positive family history, mother</td>
<td>9.7%</td>
<td>15%</td>
<td>21%</td>
</tr>
<tr>
<td>Unknown maternal history</td>
<td>2%</td>
<td>3%</td>
<td>0</td>
</tr>
<tr>
<td>ER status of primary</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>59%</td>
<td>67%</td>
<td>68%</td>
</tr>
<tr>
<td>Negative</td>
<td>36%</td>
<td>33%</td>
<td>7%</td>
</tr>
<tr>
<td>Unknown</td>
<td>4.9%</td>
<td>0</td>
<td>25%</td>
</tr>
<tr>
<td>Tumor size (median diameter in cm)</td>
<td>2.50</td>
<td>2.20</td>
<td>2.25</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lumpectomy plus RT</td>
<td>35.3%</td>
<td>43%</td>
<td>32%</td>
</tr>
<tr>
<td>Mastectomy</td>
<td>64.6%</td>
<td>57%</td>
<td>68%</td>
</tr>
<tr>
<td>Unknown</td>
<td>0.5%</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*For B-18, only patients enrolled in the adjuvant chemotherapy arm were eligible for this analysis. CBC = contralateral breast cancer; ER = estrogen receptor; N/A = not applicable; RT = radiation therapy.
Association Between Histology of Primary Breast Cancer and Contralateral Breast Cancer

Histology was missing from one primary breast cancer; therefore, the analysis of histologic association between primary and contralateral breast cancers included data from 109 patients. There was no statistically significant association between the histology of the primary breast cancer and the contralateral breast cancer (P = .683; Table 5). Of 97 patients with infiltrating ductal carcinoma in the primary breast cancer, 80 (82%) had infiltrating ductal carcinoma and 16 (16%) had infiltrating lobular carcinoma in the contralateral breast cancer. Of the eight patients with primary infiltrating lobular carcinoma, four (50%) had infiltrating ductal carcinoma and three (38%) had infiltrating lobular carcinoma in the contralateral breast cancer.

Survival

Thirty-two of the 110 patients with contralateral breast cancer had died at a median follow-up of 3.9 years after the diagnosis of contralateral disease (range = 158 days to 10.1 years). Median survival is estimated to be 9.8 years (Fig. 1). As shown in Fig. 2, there is no evidence of a difference in survival by ER status of the contralateral breast cancer (P = .923).

DISCUSSION

In the current analysis, 3.3% of patients with primary operable breast cancer developed invasive or in situ contralateral breast cancer, and there was a 6.98-year median follow-up from time of diagnosis of contralateral breast cancer. With longer follow-up, it is likely that additional cases will be reported, as demonstrated in other NSABP trials with prolonged follow-up (2,3).

In this analysis, we found that the ER status of contralateral tumors was highly associated with the ER status of the primary tumor for women who had not received adjuvant tamoxifen therapy, with a concordance rate of 81%. The association between the ER status of the primary cancer and the contralateral breast cancer for women who received tamoxifen was modest and did not reach statistical significance. In this group of women, although the magnitude of the OR is large enough (3.4) to be of clinical significance, the results could plausibly be due to chance because relatively few contralateral breast cancers occurred in these patients. This analysis also revealed no statistically significant association between the histology of a primary breast cancer and the histology of contralateral cancer. Although the number of primary infiltrating lobular carcinomas was small, 50% of the contralateral breast cancers in this group had an infiltrating ductal histology. Whether there could be an association if the sample sizes were larger is unknown.

The use of tamoxifen by women aged 50 years or older appeared to reduce the risk for developing an ER-positive contralateral breast cancer, which may explain the lower concordance rate (60%) between the primary tumor and the contralateral breast cancer in this cohort. This hypothesis is consistent with the results of randomized comparisons that have demonstrated that tamoxifen reduces the risk of ER-positive breast tumors but does not appear to reduce the risk of ER-negative disease (12,14,15,19). In the NSABP P-1 trial, tamoxifen reduced the incidence of invasive breast cancer by 49% among otherwise healthy women at high risk for the disease (14). More than 13 000 high-risk women were enrolled to this trial and randomly assigned to treatment either with tamoxifen at 20 mg/day or with placebo for 5 years. Although there was an overall decrease in the incidence of breast cancer among women receiving tamoxifen at a median follow-up of 55 months, the benefit was related to a decrease in the incidence of ER-positive disease. The risk for developing ER-positive breast cancer was reduced 69% (relative risk = 0.31, 95% CI = 0.22 to 0.45), whereas the risk for developing ER-negative disease was not statistically significantly reduced (relative risk = 1.22, 95% CI = 0.74 to 2.03) (14). Similar results were seen in the International Breast Cancer Intervention Study, a randomized trial evaluating tamoxifen at 20 mg/day for 5 years in 7132 women at high risk for developing breast cancer (15). The risk of breast cancer was reduced 32%, with effects limited to a reduction in ER-positive tumors. In the Royal Marsden Hospital trial, 2949 high-risk women were randomly assigned to tamoxifen at 20 mg/day or to placebo for up to 8 years (16). In that study, there was no statistically significant decrease in breast cancer incidence, but there were fewer ER-positive tumors among women who received tamoxifen than among women who received placebo (31 versus 44, respectively), with ER-negative tumors in 17
and 10, respectively (19). The Italian Tamoxifen Prevention Study randomly assigned 5408 women who had had a hysterectomy to treatment with tamoxifen at 20 mg/day or with placebo for 5 years and reported a slightly, but not statistically significantly, lower incidence of breast cancer for tamoxifen-treated women (18). Fewer ER-positive tumors were seen in the women who received tamoxifen than in the women who received placebo (19 versus 30, respectively), with ER-negative tumors in 17 and 10, respectively (19).

An overview of the data from all the tamoxifen prevention trials (N = 28,406) demonstrates a 30%–40% reduction in breast cancer incidence, with a statistically significant reduction of 48% in the incidence of ER-positive tumors (135 cancers among tamoxifen-treated subjects versus 267 cancers among control subjects; \( P < .001 \)) and no reduction in the incidence of ER-negative disease (hazard ratio = 1.22; \( P = .21 \)) (19). A reduction in the incidence of ER-positive, but not ER-negative, breast cancer has also been reported as a secondary endpoint in a randomized trial evaluating raloxifene in women with osteoporosis, supporting the hypothesis that ER modulators interfere with the initiation or promotion of estrogen-dependent tumors (33,34).

In a study of postmenopausal patients treated with adjuvant tamoxifen, Rutvquist and colleagues (12) reported a 40% decrease in contralateral disease among treated women relative to control subjects. The proportion of contralateral breast cancers that were ER negative was statistically significantly greater in women who had received tamoxifen than in control subjects, although the number of events was small. There are currently no strong data to support a hypothesis that tamoxifen treatment increases the risk for ER-negative contralateral disease; this result is most likely due to a decrease in the number of ER-positive contralateral breast cancers with tamoxifen treatment (35).

![Fig. 1. Kaplan–Meier curve showing survival of patients enrolled in National Surgical Adjuvant Breast and Bowel Project B-18 (adjuvant chemotherapy arm only), B-22, and B-25 randomized trials after a diagnosis of contralateral breast cancer.](https://academic.oup.com/jnci/article-abstract/96/7/516/2521186)

It cannot be definitively concluded that tamoxifen provides no benefit for patients with an ER-negative primary cancer because of the small number of patients in the current sample and in the worldwide literature. It is possible that tamoxifen could reduce the risk of contralateral breast cancer in women with ER-negative disease because some of these patients will develop an ER-positive contralateral breast cancer. However, randomized trials to date have not shown a reduction in the risk of contralateral breast cancer with tamoxifen in this patient population (20,36). NSABP-B23 enrolled 2008 patients with lymph node-negative, ER-negative breast cancer who were randomly assigned to chemotherapy with or without tamoxifen (20). At 5 years, the contralateral breast cancer incidence rate was 2%, regardless of tamoxifen administration. It would be difficult to implement a trial to test the hypothesis that tamoxifen reduces the incidence of contralateral breast cancer in patients with ER-negative primary breast cancers, given the low event rates. For example, the current analysis found that 30% of patients with an ER-negative primary who did not receive tamoxifen developed an ER-positive contralateral breast cancer, representing a subgroup that could potentially benefit from tamoxifen therapy. If, in fact, the overall reduction in contralateral breast cancers is 50% (the magnitude seen in the P-1 trial), but tamoxifen had no effect on the development of ER-negative contralateral breast cancer, then tamoxifen would be considered successful in decreasing contralateral breast cancers in the ER-negative primary group by 15%. To reliably detect such a small benefit would require a study large enough and with sufficient follow-up to diagnose approximately 1190 contralateral breast cancers. Furthermore, any gains in preventing contralateral breast cancer would have to be balanced against the increased risks for thromboembolic disease and endometrial cancer associated with treatment.

There are several potential limitations to this analysis. The use of tamoxifen was not randomized and was predicated on patient age rather than the ER status of the primary tumor. Therefore, the generalizability of these results to women under...
the age of 50 who received tamoxifen is not known. In addition, among 138 cases of invasive contralateral breast cancer, the ER status of either the primary or contralateral tumor was unknown for 28, although every attempt was made to collect these data. Because the characteristics at study entry of these 28 patients did not differ from those of the overall group or the analyzed group, it is unlikely that the missing data affected the results. Also, the analysis may have been strengthened if a central laboratory for receptor testing had been used. The NSABP has recently reported a wide variation in ER classification when the results from outside labs are compared with those from a centralized laboratory. In NSABP B-24, outside laboratories reported that 30% of ductal carcinoma in situ samples were ER negative, whereas 20% were identified as ER negative in the central laboratory ($P = .016$) (37). The potential for false negatives in various laboratories has implications for treatment and suggests that some patients who really have ER-positive tumors may not be receiving tamoxifen when indicated. This finding highlights the need for standardized methodology in determining ER status to ensure appropriate classification and treatment of patients.

Whether contralateral breast cancer represents a multicentric process, manifested by multiple primary tumors arising in a common milieu, a de novo primary cancer, or a contralateral recurrence remains to be determined and may vary from case to case. Advances in molecular techniques, such as karyotypic and gene expression analyses, will aid in addressing this question. These tools have been used to evaluate the clonal relationship between ipsilateral breast tumors (38) and between primary breast tumors and metastatic disease (39). Similar analyses could be performed to further elucidate the nature of contralateral disease relative to primary breast cancer, with the goal of designing improved preventive and therapeutic strategies. At this time, the available data indicate that the ER status of a primary breast cancer correlates with the ER status of a subsequent contralateral tumor. The use of tamoxifen decreases the incidence of ER-positive contralateral tumors and therefore alters the ER status concordance between primary and contralateral tumors. Although this finding suggests a theoretical benefit to treating all women with breast cancer with adjuvant tamoxifen, including those with an ER-negative primary, in an effort to reduce contralateral disease, the current data indicate that the benefit would likely be very marginal.

REFERENCES


**NOTE**

Manuscript received August 27, 2003; revised February 9, 2004; accepted March 2, 2004.