Tamoxifen and risk of contralateral breast cancer in BRCA1 and BRCA2 mutation carriers: a case-control study

Steven A Narod, Jean-Sébastien Brunet, Parviz Ghadirian, Mark Robson, Ketil Heimdal, Susan L Neuhausen, Dominique Stoppa-Lyonnet, Caryn Lerman, Barbara Pasini, Patricia de los Ríos, Barbara Weber, Henry Lynch, for the Hereditary Breast Cancer Clinical Study Group*

**Summary**

**Background** Women with a mutation in BRCA1 or BRCA2 have a high risk of developing breast cancer and of contralateral breast cancer after the initial diagnosis of breast cancer. Tamoxifen protects against contralateral breast cancer in the general population, but whether it protects against contralateral breast cancer in BRCA1 or BRCA2 mutation carriers is not known.

**Methods** We compared 209 women with bilateral breast cancer and BRCA1 or BRCA2 mutation (bilateral-disease cases), with 384 women with unilateral disease and BRCA1 or BRCA2 mutation (controls) in a matched case-control study. Age and age at diagnosis of breast cancer (range 24–74 years) were much the same in bilateral-disease cases and controls, and both groups had been followed up for the same time for a second primary breast cancer. History of tamoxifen use for first breast cancer was obtained by interview, or by self-administered questionnaire.

**Findings** The multivariate odds ratio for contralateral breast cancer associated with tamoxifen use was 0·50 (95% CI 0·26–0·80). Tamoxifen protected against contralateral breast cancer for carriers of BRCA1 mutations (odds ratio 0·38, 95% CI 0·19–0·74) and for those with BRCA2 mutations (0·63, 0·20–1·50). In women who used tamoxifen for 2–4 years, the risk of contralateral breast cancer was reduced by 75%. A reduction in risk of contralateral breast cancer was also seen with oophorectomy (0·42, 0·22–0·83) and with chemotherapy (0·40, 0·26–0·60).

**Interpretation** Tamoxifen use reduces the risk of contralateral breast cancer in women with pathogenic mutations in the BRCA1 or BRCA2 gene. The protective effect of tamoxifen seems independent of that of oophorectomy.

**Lancet** 2000; 356: 1876–81

---

**Introduction**

Many familial breast cancers are hereditary, and might be associated with germline mutations in the BRCA1 or BRCA2 gene.14 Breast and ovarian cancers in families with several affected members are likely to be hereditary.15 In such families in women who carry deleterious BRCA1 or BRCA2 mutations the lifetime risk of breast cancer is estimated to be as high as 80%,1 2 but estimates based on unselected cases of breast cancer are lower than 80%.1,14 In the 10 years after diagnosis of breast cancer in a BRCA1 or BRCA2 mutation carrier, the risk of contralateral breast cancer is about 35%.1,14 Strategies for reducing the risk of primary and contralateral breast cancer include prophylactic mastectomy and chemoprevention.1,15 Tamoxifen reduces the risk of primary invasive and premalignant breast cancer in women at high-risk and of contralateral breast cancer in unselected women.10 However, the use of tamoxifen has not yet been assessed in known carriers of BRCA1 or BRCA2 mutations. To investigate the potential benefit of tamoxifen in the reduction of risk of contralateral breast cancer among BRCA1 or BRCA2 mutation carriers, we studied women with bilateral hereditary breast cancer and age-matched controls with unilateral hereditary breast cancer.

**Methods**

**Patients and controls** Information about patients with hereditary breast cancer was submitted to the study centre by investigators at each of 34 contributing centres in eight countries. These centres were requested to complete forms for all known cases of female breast cancer carrying a verified BRCA1 or BRCA2 mutation. Most of these patients were identified through genetic counselling and risk-assessment programmes offered to women from high-risk families. The data centre received information for 1243 cases of invasive breast cancer in carriers of pathogenic BRCA1 or BRCA2 mutations.

Of the 1243 cases, 296 (24%) had bilateral breast cancer. 83 (28%) cases with bilateral disease were excluded from our study: 28 (10%) who had their first cancer diagnosed before Jan 1, 1970 (ie, before tamoxifen was in use); 39 (13%) who had contralateral cancer within 1 year of the initial diagnosis; 14 (5%) who had ovarian cancer diagnosed before contralateral breast cancer; and two (0·6%) who had a contralateral mastectomy before the development of contralateral breast cancer. Synchronous bilateral cases were excluded because the patient would not be able to take tamoxifen before the onset of the contralateral cancer. A control was not identified for four cases with bilateral disease who were therefore excluded from the analyses. Thus, 209 (71%) eligible patients with bilateral breast cancer were included.

Controls were selected from women with unilateral breast cancer in the registry database. They were born within 5 years of the birth date of the bilateral-disease case, and diagnosed with breast cancer at an age within 5 years of age of first diagnosis of breast cancer of the case. Cases and controls were carriers of mutations in the same gene (BRCA1 or BRCA2) and were matched for residence (ie,
for mutations in exon 11 of 

Techniques, and all mutations were confirmed by direct 

Mutation analysis. 

Because risk factor information was obtained by 

The years of diagnosis of the initial and contralateral breast 

cancer were recorded. Women were asked if they had 

received tamoxifen for first breast cancer, and if so, the 

dose, dates, and duration of treatment: tamoxifen use was 

defined as that given as treatment for the initial breast 

cancer, and not for the recurrent cancer. Women were also 

asked to report on the type of surgical treatment they 

received (lumpectomy, unilateral mastectomy, or bilateral 

mastectomy). They were asked if they had undergone 

bilateral oophorectomy, before cancer diagnosis or 

thereafter, and if they had had chemotherapy or 

radiotherapy for the initial breast cancer. Whether patients 

smoked, their reproductive history, and ethnic origin were 

also recorded.

**Study protocol**

Bilateral-disease cases and controls completed a questionnaire that asked about medical and surgical treatment of their initial breast cancer. In some centres the questionnaire was administered by telephone interview.

**Statistical analysis**

A matched case-control analysis was done. The frequency and mean duration of tamoxifen use were compared between bilateral-disease cases and controls. The duration of tamoxifen use was compared by Wilcoxon’s two-sample test. The univariate odds ratios and p values for contralateral breast cancer associated with tamoxifen use were calculated with conditional logistic regression. Cases with bilateral disease and controls were also compared for parity, smoking history, oophorectomy, and other medical treatments with Wilcoxon’s two-sample test for continuous variables and univariate conditional logistic regression for categorical variables.

To estimate the odds ratio for contralateral breast cancer associated with tamoxifen use, after adjustment for the other covariates, including other treatments received, we used a multivariate conditional logistic regression model.

### Table 1: Characteristics of cases with bilateral disease and of controls

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cases with bilateral disease (n=209)</th>
<th>Controls (n=384)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at 1st breast cancer (years)*</td>
<td>39.4 (8.9)</td>
<td>40.6 (8.8)</td>
<td>.87</td>
</tr>
<tr>
<td>Year of diagnosis *</td>
<td>1964-5 (10.5)</td>
<td>1964-5 (10.4)</td>
<td>.41</td>
</tr>
<tr>
<td>Year of interview*</td>
<td>1997-9 (1.3)</td>
<td>1996-9 (1.4)</td>
<td>.15</td>
</tr>
<tr>
<td>Parity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>31 (15%)</td>
<td>40 (10%)</td>
<td>.01</td>
</tr>
<tr>
<td>1</td>
<td>88 (42%)</td>
<td>152 (40%)</td>
<td>.11</td>
</tr>
<tr>
<td>&gt;2</td>
<td>66 (32%)</td>
<td>142 (37%)</td>
<td>.05</td>
</tr>
<tr>
<td>Place of residence†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canada</td>
<td>47 (23%)</td>
<td>81 (21%)</td>
<td>.05</td>
</tr>
<tr>
<td>USA</td>
<td>98 (47%)</td>
<td>194 (51%)</td>
<td>.006</td>
</tr>
<tr>
<td>Europe</td>
<td>54 (26%)</td>
<td>159 (39%)</td>
<td>.007</td>
</tr>
<tr>
<td>Race or ethnic group‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ashkenazi Jewish</td>
<td>61 (29%)</td>
<td>128 (33%)</td>
<td>.01</td>
</tr>
<tr>
<td>French-Canadian</td>
<td>17 (7%)</td>
<td>28 (7%)</td>
<td>.03</td>
</tr>
<tr>
<td>Other white</td>
<td>123 (59%)</td>
<td>221 (57%)</td>
<td>.003</td>
</tr>
<tr>
<td>Non-white</td>
<td>10 (5%)</td>
<td>7 (2%)</td>
<td>.50</td>
</tr>
<tr>
<td>Smoking history§</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>106 (50%)</td>
<td>212 (55%)</td>
<td>.04</td>
</tr>
<tr>
<td>Before 1st breast cancer</td>
<td>39 (21%)</td>
<td>76 (22%)</td>
<td>.05</td>
</tr>
<tr>
<td>After 1st breast cancer</td>
<td>44 (22%)</td>
<td>65 (17%)</td>
<td>.01</td>
</tr>
</tbody>
</table>

*Values are mean (SD) or †number (%). ‡Smoking information was missing for 20 bilateral-disease cases and 45 controls.

### Table 2: Factors associated with treatment of first breast cancer

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Cases with bilateral disease (n=209)</th>
<th>Controls (n=384)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tamoxifen use*</td>
<td>58 (28%)</td>
<td>107 (28%)</td>
<td>.18</td>
</tr>
<tr>
<td>Tamoxifen duration (years)*</td>
<td>0</td>
<td>187 (90%)</td>
<td>303 (79%)</td>
</tr>
<tr>
<td>&gt;2</td>
<td>13 (6%)</td>
<td>50 (13%)</td>
<td>.02</td>
</tr>
<tr>
<td>2-4</td>
<td>3 (1%)</td>
<td>19 (5%)</td>
<td>.04</td>
</tr>
<tr>
<td>&gt;4</td>
<td>4 (3%)</td>
<td>12 (3%)</td>
<td>.85</td>
</tr>
<tr>
<td>Oophorectomy*</td>
<td>Ever</td>
<td>13 (6%)</td>
<td>57 (15%)</td>
</tr>
<tr>
<td>Before cancer</td>
<td>5 (2%)</td>
<td>19 (5%)</td>
<td>.10</td>
</tr>
<tr>
<td>After cancer</td>
<td>8 (4%)</td>
<td>38 (10%)</td>
<td>.01</td>
</tr>
<tr>
<td>Surgery*</td>
<td>Lumpectomy</td>
<td>73 (36%)</td>
<td>169 (45%)</td>
</tr>
<tr>
<td>Mastectomy</td>
<td>134 (68%)</td>
<td>209 (55%)</td>
<td>.07</td>
</tr>
<tr>
<td>Radiotherapy*</td>
<td>101 (48%)</td>
<td>212 (55%)</td>
<td>.11</td>
</tr>
<tr>
<td>Chemotherapy*</td>
<td>84 (42%)</td>
<td>234 (61%)</td>
<td>.0001</td>
</tr>
</tbody>
</table>

*Values are number (%). Information on type of surgery was missing for five cases with bilateral disease and six controls. All p values were calculated with a univariate conditional logistic regression.
To control for possible confounding, ethnic group, smoking, and parity were also included in the multivariate analysis. To estimate the protective effect of tamoxifen separately for \textit{BRCA1} and \textit{BRCA2} carriers, odds ratio estimates were generated for these subgroups with the matched-pair subsets. All calculations were done with the SAS (version 8.0) statistical package.

**Results**

The characteristics of the 209 cases with bilateral disease and 384 unilateral disease controls were much the same (table 1). The average time from first cancer to diagnosis of contralateral cancer was 6.1 years for the cases with bilateral disease. The average period of follow-up was 9.7 years for controls, and every control was followed up for as long as the matched case.

Table 2 shows tamoxifen use, which was higher in controls than in cases with bilateral disease. In women who had taken tamoxifen the likelihood of developing cancer in the contralateral breast was reduced (table 3). The results of the multivariate analysis, controlling for other treatments, ethnic group, parity, and smoking, were mostly similar to those of univariate analysis (table 3). Among tamoxifen users, the average duration of use for bilateral-disease cases was 3.27 (SD 3.01) years, and was 2.67 (2.14) years for controls (p=0.40). The average age at first use of tamoxifen was 43.7 (12.0) years for the cases with bilateral disease and 45.7 (9.0) years for the controls.

There were 476 patients with \textit{BRCA1} mutations (168 cases with bilateral disease and 308 controls) and 117 with \textit{BRCA2} mutations (41 bilateral-disease cases and 76 controls). \textit{BRCA1} carriers were diagnosed with their first cancer at a mean of 38.9 (8.3) years and \textit{BRCA2} mutation carriers at 45.2 (9.3) years. Tamoxifen use was reported for 64 (13%) \textit{BRCA1} mutation carriers and for 39 (33%) \textit{BRCA2} mutation carriers. The protective effect of tamoxifen was apparent in \textit{BRCA1} and \textit{BRCA2} mutation carriers; of the \textit{BRCA1} mutation carriers the odds ratio was 0.36 (0.19–0.74) and of the \textit{BRCA2} mutation carriers the odds ratio was 0.63 (0.30–1.50).

The median year of diagnosis of first breast cancer for the 593 patients was 1986 (range 1970–88). Tamoxifen use was reported by 23 (4%) women diagnosed before 1980, by 91 (15%) diagnosed from 1980 to 1989 and by 158 (26%) diagnosed since 1990. The odds ratio for second primary cancer associated with tamoxifen use was 0.30 (0.04–2.48) for women treated before 1980, 0.29 (0.12–0.71) for those treated from 1980 to 1989, and 0.68 (0.33–1.40) for those treated since 1990. Tamoxifen use was associated with odds ratios of 0.36 (0.17–0.75) and 0.71 (0.30–1.69) for women diagnosed in North America and Europe, respectively. However, the two odds ratios did not differ significantly (p value for interaction=0.21). The protective effect of tamoxifen was greater in North America than in Europe (data not shown). The European patients differed from American patients in that they had a higher proportion of \textit{BRCA1} mutations (56 [88%] vs 75 [77%]), a younger age at first cancer diagnosis (38.5 years [SD 7.4] vs 40.8 years [9.3]), and a more recent diagnosis of first primary breast cancer (March/April, 1987 vs May/June, 1985).

The protective effect of tamoxifen was slightly greater for women who were diagnosed with the second breast cancer at or after age 50 years (0.39, 0.14–1.08) than for those who were diagnosed with contralateral breast cancer before age 50 (0.47, 0.25–0.88). The protective effect of tamoxifen increased with duration of tamoxifen use up to 4 years (table 3). We recorded a small increase in risk of contralateral breast cancer in the multivariate analysis for those who had used tamoxifen for more than 4 years, but there were only six cases with bilateral disease and 12 controls in this subgroup.

Oestrogen-receptor status was available for only a few patients. In such patients with bilateral disease 16 of 56 (29%) who had first primary cancers and 22 of 74 (30%) who had contralateral breast cancers were oestrogen-receptor positive. Of the women who did not receive tamoxifen, 17 of 64 (27%) contralateral tumours were oestrogen-receptor positive, and of those who received tamoxifen, five of ten (50%) contralateral tumours were oestrogen-receptor positive (odds ratio 2.77 [95% CI 0.71–10.8]; p=0.15).

We also noted a difference in the frequency of oophorectomy between cases with bilateral disease and controls (table 2). Oophorectomies done before menopause might affect the subsequent breast cancer risk. Among 185 women diagnosed with first breast cancer before age 50 years and their matched controls, the odds ratio associated with oophorectomy was 0.31 (0.15–0.67). The protective effect of oophorectomy was much less for those who had their first breast cancer at or after age 50 years (0.85, 0.22–3.36). However, the interaction between oophorectomy and age of breast cancer diagnosis was not significant (p=0.23). The protective effect of tamoxifen was present in the subgroups of women with oophorectomy (0.36, 0.07–1.81) and without oophorectomy (0.49, 0.28–0.83). The odds ratio for tamoxifen use combined with oophorectomy, compared with no tamoxifen or oophorectomy was 0.16 (0.04–0.69).

We showed a protective effect in women who were initially treated with chemotherapy for the first breast cancer. These women had a 60% reduction in risk of contralateral cancer (table 3). The protective effect of chemotherapy did not seem to be due to its effect on ovariatic function; it was present in women without ovaries (0.43, 0.12–1.54) and in those with their ovaries intact (0.45, 0.31–0.58).

For tamoxifen use, oophorectomy, and chemotherapy the protective effect on the risk of contralateral breast cancer was analysed according to time elapsed since initial diagnosis (table 4). Chemotherapy greatly reduced the risk of diagnosis.
of contralateral breast cancers within 2 years of treatment but the risk rose after 10 years. The main effect of chemotherapy therefore seemed to be the eradication of prevalent, subclinical contralateral breast cancers. The protective effect of tamoxifen did not persist longer than 10 years (table 4); by contrast, the protective effect of oophorectomy was long lasting. This difference is consistent with the notion that oophorectomy permanently reduces endogenous oestrogen exposure, whereas the effect of tamoxifen on reducing hormone exposure is temporary. However, the number of patients in each of these subcategories was fairly small, and the confidence limits of the estimates for the subgroups overlap. We examined whether tamoxifen use, oophorectomy, and by chemotherapy were independent protective factors, using a conditional multivariate logistic regression analysis. All three treatments were independently protective (table 3), and the effects were present after adjustment for ethnic group, smoking, and parity.

**Discussion**

Our results suggest that the risk of contralateral breast cancer is reduced by 50% in carriers of BRCA1 and BRCA2 mutations when tamoxifen is used for the treatment of the initial breast cancer. Women and their physicians were not aware of the BRCA1 or BRCA2 carrier status at the time of initial diagnosis. Tamoxifen use was reported more often by BRCA2 mutation carriers than by BRCA1 mutation carriers. This difference is to be expected, in view of the older age of onset of breast cancer in the BRCA2 mutation carriers than in the BRCA1 mutation carriers. Furthermore, breast tumours that arise in BRCA1 mutation carriers are oestrogen-receptor negative, whereas BRCA2-mutation-associated tumours are typically oestrogen-receptor positive. The effect of tamoxifen in the National Surgical Adjuvant Breast and Bowel (NSABP) P1 trial seemed to be limited to the prevention of oestrogen-receptor positive tumours, and some workers have predicted that anti-oestrogen therapy will therefore be ineffective as chemoprevention for women with BRCA1 mutations. We have shown that tamoxifen is effective in both BRCA1 and BRCA2 mutation carriers. Furthermore, in a subset of the data we noted an association between oestrogen-receptor status of the contralateral breast cancer and past tamoxifen use. A greater proportion of the contralateral breast cancers were oestrogen-receptor positive in women with a history of tamoxifen use than in those with no past use, but the samples sizes were small. The NSABP P1 trial did not provide data on the subset of BRCA1 and BRCA2 mutation carriers, and perhaps only a small number of participants in that study were mutation carriers.

There are several reasons to believe that breast cancer risk in women with BRCA1 or BRCA2 mutations might be reduced by blocking the activity of endogenous oestrogens. The incidence of breast cancer in BRCA1 mutation carriers declines after age 50, whereas the risk in women with BRCA1 and BRCA2 mutation carriers, pregnancy increases the risk of early-onset breast cancer (by contrast with non-carriers for whom the effect of pregnancy is protective). Brunet and colleagues reported that smoking protected against breast cancer in BRCA1 and BRCA2 mutation carriers. This effect is probably an anti-oestrogenic mechanism. One of the functions of the normal BRCA1 protein is proposed to be the reduction of the proliferative response of the breast epithelium during periods of oestrogen exposure. Further, tamoxifen might reduce breast cancer risk through mechanisms other than receptor-mediated oestrogen blockade. This hypothesis is consistent with our finding that tamoxifen seems to be protective in women who have undergone an oophorectomy and the protective effects of oophorectomy and tamoxifen seem to be independent and additive.

We believe that our study design is the best way to address this issue. We could not analyse this dataset by a historical cohort approach, because genetic testing was offered only to living women, and, in many instances, was offered a considerable time after diagnosis. Additionally, women with bilateral cancer were more likely to have been offered genetic testing than were unilateral cases. Therefore a cohort study would be biased towards the inclusion of both long-term survivors and bilateral cases. We have kept to a minimum the possible effect of survivor bias, because our design required the controls were followed up for at least as long as the matched case. If genetic testing becomes widespread our findings might be confirmed by a cohort of incident cases, but these data will not be available for many years. Because of the difficulty in establishing carrier status for deceased women, our case-control study was restricted to living patients with breast cancer.

Generally, the women completed the questionnaires 10 years after their initial diagnosis of breast cancer, and because of this time difference our findings, which are based on breast cancer survivors, might not represent the population of patients in general. For example, if women who develop contralateral breast cancer after using tamoxifen have a poor survival relative to those with bilateral breast cancer who have not taken this drug, our estimate of the protective effect of tamoxifen would be too large. However, if tamoxifen use is associated with improved survival in this population (eg, if it is preferentially given to women with less aggressive tumours, or if the drug confers a survival advantage), we would have underestimated the true positive effect of tamoxifen.

We believe that the observed reduction in contralateral breast cancer risk is attributable to tamoxifen use and not to systemic differences in the risk profiles between the cases with bilateral disease and controls. These two groups were similar in terms of year of birth and age of cancer onset. Women with primary breast cancer who were oestrogen-receptor positive were more likely to have been prescribed tamoxifen than those who were oestrogen-receptor negative. However, the prognostic features of the first cancer should not affect the risk of contralateral breast cancer. In a large meta-analysis, tamoxifen was equally effective in prevention of contralateral breast cancer in women with
For personal use only. Not to be reproduced without permission of The Lancet.
Registry, and the Utah Department of Health. MR is the recipient of an American Cancer Society Physicians Training Award PRTA-38.

References