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Adjuvant Hormonal Therapy for Breast Cancer and Risk of Hormone Receptor–Specific Subtypes of Contralateral Breast Cancer

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Abstract

Compared with the breast cancer risk women in the general population have, breast cancer survivors have a substantially higher risk of developing a second primary contralateral breast cancer. Adjuvant hormonal therapy reduces this risk, but preliminary data indicate that it may also increase risk of hormone receptor–negative contralateral tumors. We conducted a population-based nested case-control study including 367 women diagnosed with both first primary estrogen receptor (ER)–positive invasive breast cancer and second primary contralateral breast cancer and 728 matched control women diagnosed only with a first breast cancer. Data on adjuvant hormonal therapy, other treatments, and breast cancer risk factors were ascertained through telephone interviews and medical record abstractions. Two-sided statistical tests using conditional logistic regression were conducted to quantify associations between adjuvant hormonal therapy and risk of hormone receptor–specific subtypes of contralateral breast cancer (n = 303 ER+ and n = 52 ER− cases). Compared with women not treated with hormonal therapy, users of adjuvant tamoxifen for ≥5 years had a reduced risk of ER+ contralateral breast cancer [odds ratio, 0.4; 95% confidence interval (CI), 0.3–0.7], but a 4.4-fold (95% CI, 1.03–19.0) increased risk of ER− contralateral breast cancer. Tamoxifen use for <5 years was not associated with ER− contralateral breast cancer risk. Although adjuvant hormonal therapy has clear benefits, risk of the relatively uncommon outcome of ER− contralateral breast cancer may now need to be tallied among its risks. This is of clinical concern given the poorer prognosis of ER− compared with ER+ tumors. [Cancer Res 2009;69(17):6865–70]

Introduction

Breast cancer survivors have a two to six times greater risk of developing a second primary contralateral breast cancer than women in the general population have of developing a first breast cancer (1). Numerous randomized trials of adjuvant tamoxifen therapy have documented substantial reductions in the risk of three clinically important breast cancer outcomes, specifically second primary contralateral breast cancer, recurrence of the primary cancer, and mortality. A meta-analysis of 55 of these trials indicates that use of tamoxifen for 5 years reduces the risk of contralateral breast cancer by 47% (2). Although adjuvant tamoxifen unequivocally reduces subsequent risk of estrogen receptor (ER)–positive (ER+) contralateral breast cancer, it is possible that it may also increase the risk of ER-negative (ER−) disease. Given the heterogeneous nature of ER expression in breast tumors (3), it is plausible that although tamoxifen selectively inhibits the proliferation of ER+ tumor cells, it may consequently foster an environment in which ER− tumor cells can thrive (4). This phenomenon has been observed both in animal models (5) and in humans (6). In 2001, we published the first report of a possible concomitant heightened risk of ER− contralateral breast cancer. Specifically, compared with nonusers, we observed a 4.9-fold increased risk of ER− contralateral breast cancer for tamoxifen users (7).

Since our report, few studies have further addressed this question of differential effects of tamoxifen on ER+ versus ER− contralateral second primary; however, those that have find results consistent with our initial finding. In a combined analysis of data from three National Surgical Adjuvant Breast and Bowel Project trials of adjuvant tamoxifen therapy for breast cancer, the proportion of ER− contralateral tumors diagnosed among 74 women with ER+ first breast cancers varied considerably by exposure to adjuvant tamoxifen; 43% of contralateral tumors among tamoxifen users were ER− compared with only 11% of those diagnosed among nonusers of tamoxifen (8). Similarly, three institution-based series conducted in Detroit, Michigan (n = 144 contralateral cases; ref. 9), Houston, Texas (n = 193 contralateral cases; ref. 10), and the Netherlands (n = 150 contralateral cases; ref. 11) all found that the proportion of ER− contralateral tumors diagnosed among tamoxifen users was higher than that among nonusers of tamoxifen (55% versus 10% in the Detroit study; 53% versus 12% in the Houston study; and 37% versus 18% in the Dutch study). However, all four studies had somewhat limited sample sizes, did not evaluate risk by duration of tamoxifen use, and did not incorporate multivariate-adjusted statistical modeling of this relationship.

Our initial study had several limitations, specifically a lack of information on duration of tamoxifen use, other breast cancer treatment details, and potentially relevant covariates such as body mass index (BMI) and family history of breast cancer. We recently completed a population-based nested case-control study in the Seattle-Puget Sound metropolitan area designed specifically to evaluate the relationship between adjuvant tamoxifen therapy and risk of second primary contralateral breast cancer by hormone receptor status and to overcome the aforementioned limitations. This issue is of clinical and public health importance given the frequent use of adjuvant tamoxifen therapy by breast cancer patients, the growing number of breast cancer survivors, their appreciable risk of developing second primary contralateral breast cancer, and the morbidity and mortality associated with second primary contralateral breast cancer, particularly those that are hormone receptor negative.

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Table 1. Characteristics of controls and contralateral breast cancer cases

Characteristic	Controls (n = 727)	Contralateral cases (n = 367)
	n (%)	n (%)
Demographic characteristics		
Age at first breast cancer diagnosis, y		
40–49	137 (18.8)	71 (19.3)
50–59	198 (27.2)	97 (26.4)
60–69	223 (30.7)	112 (30.5)
70–79	169 (23.2)	87 (23.7)
Age at reference date (age at contralateral breast cancer diagnosis for cases), y		
40–59	218 (30.0)	106 (28.9)
60–69	231 (31.8)	117 (31.9)
70–79	210 (28.9)	104 (28.3)
80–88	68 (9.4)	40 (10.9)
Year of first breast cancer diagnosis		
1990–1993	263 (36.2)	133 (36.2)
1994–1997	246 (33.8)	122 (33.2)
1998–2001	164 (22.6)	85 (23.2)
2002–2005	54 (7.4)	27 (7.4)
Months between first breast cancer diagnosis and reference date		
6–11	44 (6.1)	23 (6.3)
12–23	108 (14.9)	54 (14.7)
24–59	236 (32.5)	116 (31.6)
60–119	261 (35.9)	133 (36.2)
≥120	78 (10.7)	41 (11.2)
Race/ethnicity		
Non-Hispanic White	662 (91.3)	336 (92.1)
Asian/Pacific Islander	28 (3.9)	12 (3.3)
African American	19 (2.6)	9 (2.5)
Native American	10 (1.4)	5 (1.4)
Hispanic White	6 (0.8)	3 (0.8)
Missing	2	2
Treatments for first primary breast cancer		
Received radiation therapy for first primary breast cancer		
No	248 (34.1)	131 (35.7)
Yes	479 (65.9)	236 (64.3)
Received chemotherapy for first primary breast cancer		
No	534 (73.6)	272 (74.5)
Yes	192 (26.4)	93 (25.5)
Missing	1	2

Participants and Methods

We conducted a population-based nested case-control study where the underlying cohort from which cases and controls were drawn consisted of all 17,628 women diagnosed with a first primary invasive, stage I to IIIB, ER+ breast cancer at age 40 to 79 y in the four county Seattle-Puget Sound region (including King, Pierce, Snohomish, and Thurston counties) from January 1, 1990 to September 30, 2005. This cohort was identified through the Cancer Surveillance System (CSS), the population-based cancer registry that serves western Washington and has participated in the National Cancer Institute's (NCI) Surveillance, Epidemiology and End Results (SEER) program since 1974. It is estimated that ~99% of all incident cancer cases diagnosed in the catchment area of CSS are ascertained. Women with stage IIIC and IV breast cancers were excluded from the cohort because our outcome of interest was second primary contralateral breast cancer, and tumors of this stage have high recurrence and mortality rates. The cohort was restricted to women with ER+ disease because our primary exposure of interest was tamoxifen, which is only recommended for the treatment of hormone receptor–positive disease. Women diagnosed at <40 y of age were excluded because adjuvant hormonal therapy is not always recommended for premenopausal women, and women ≥80 y of age were excluded to help insure that cohort members had a sufficient number of years at risk to develop contralateral breast cancer. In addition, women were enrolled regardless of vital status to overcome the bias that would have resulted from excluding potentially eligible participants who died before attempted study contact.

Second primary invasive contralateral breast cancer cases diagnosed among women in our cohort were identified through CSS, which records information on all primary cancers, regardless of their sequence. These cases were defined as women who developed invasive cancer in the breast contralateral to their first breast cancer 6 mo or more after their first breast cancer diagnosis from July 1, 1990 to March 31, 2007 in our four county catchment area. Controls were individually matched 2:1 to cases on age, year of diagnosis, county at first diagnosis, race/ethnicity, SEER historic stage of first breast cancer (localized versus regional), and survival at least through the time their matched case was diagnosed with contralateral breast cancer. In addition, controls had to reside in their county of diagnosis from their breast cancer diagnosis to at least the duration between their matched case's first and second breast cancer diagnoses.

Potential study participants were approached for this study through a letter describing the study's purpose and procedures followed several days

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Table 1. Characteristics of controls and contralateral breast cancer cases (Cont'd)

Characteristic	Controls (n = 727)	Contralateral cases (n = 367)
	n (%)	n (%)
Tumor Characteristics		
AJCC stage		
I	495 (68.1)	239 (65.1)
II or III	232 (31.9)	128 (34.9)
Lymph node involvement		
No	558 (76.8)	273 (74.4)
Yes	169 (23.2)	94 (25.6)
Tumor size, cm		
≤1.0	247 (34.8)	116 (33.0)
1.1–2.0	315 (44.4)	143 (40.7)
>2.0	148 (20.8)	92 (26.2)
Missing	17	16
Patient characteristics		
First -degree family history of breast cancer at first breast cancer diagnosis		
No	512 (74.5)	237 (70.5)
Yes	175 (25.5)	99 (29.5)
Missing	40	31
No. of full-term pregnancies at first breast cancer diagnosis		
0	105 (14.9)	58 (16.4)
1–2	303 (42.9)	156 (44.1)
≥3	299 (42.3)	140 (39.5)
Missing	20	13
BMI at first breast cancer diagnosis, kg/m^2		
<25.0	317 (44.4)	133 (37.3)
25.0–29.9	213 (30.0)	116 (32.5)
≥30.0	183 (25.7)	108 (30.3)
Missing	14	10
BMI at reference date, kg/m^2		
<25.0	254 (39.2)	110 (35.4)
25.0–29.9	221 (34.1)	95 (30.5)
≥30.0	174 (26.7)	106 (34.1)
Missing	78	56
Ever used menopausal hormone therapy at first breast cancer diagnosis		
Never	343 (49.7)	172 (50.9)
Former	72 (10.4)	40 (11.8)
Current estrogen user	144 (20.9)	71 (21.0)
Current estrogen+progestin user	131 (19.0)	55 (16.3)
Missing	37	29

Abbreviation: AJCC, American Joint Committee on Cancer.

later by a telephone call from one of our trained interviewers to answer questions and to either perform or schedule the study interview if the participant was willing. Eligible participants were included regardless of vital status, so deceased women were enrolled through a waiver of consent granted by the Fred Hutchinson Cancer Research Center's Institutional Review Board, and enrolled alive women all provided verbal informed consent. A total of 446 eligible cases were identified of which 369 (83%) were enrolled, and a total of 982 eligible controls were identified of which 734 (75%) were enrolled. Use of adjuvant hormonal therapy was known for 367 cases and 727 controls.

Data on demographic, epidemiologic, and clinical factors were ascertained from two sources, structured interviewer administered telephone questionnaires and a detailed medical record review. The telephone interview queried women on their reproductive history, family history of breast cancer, medical history, use of exogenous hormones, life-style factors, anthropometric characteristics, and breast cancer treatments they received. Women were asked to recall their exposures before their assigned reference date which for cases was the date of their contralateral breast cancer diagnosis and for controls was the date of their matched case's contralateral breast cancer diagnosis. Data from medical records were abstracted from multiple sources including hospitals, oncology practices, and primary care practices as needed to obtain complete data on breast cancer treatments, clinical and pathologic tumor characteristics, anthropometric characteristics, breast cancer risk factors, and medical history. For the 22% of cases and controls (n = 246) that were deceased at enrollment, data were only collected from medical records. For deceased women in our study, complete data for ever use of tamoxifen, first degree family history of breast cancer, BMI, use of menopausal hormone therapy, and parity were abstracted for 97%, 90%, 90%, 90%, and 88% of these women, respectively.

Our primary exposure of interest was use of adjuvant tamoxifen therapy. We collected detailed information in both our telephone interviews and medical record reviews on use of all forms of adjuvant hormonal therapy for breast cancer including drug names and doses, frequency of use, start and stop dates, side effects and complications, and any interruptions or changes

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in patterns of use. With this information, we computed total durations of use of any adjuvant hormonal therapy and use of tamoxifen specifically. Given the era in which this study was conducted, almost all users of adjuvant hormonal therapy were tamoxifen users (94%). When self-reported data on adjuvant hormonal therapy conflicted with the data ascertained from our medical record reviews, in our analyses, we prioritized the medical record data over the self-reported data. This is because the medical record data were viewed to have a higher validity considering the advanced age of many participants at study contact and that many were required to recall exposures >10 y in the past. Nevertheless, the agreement between data from the two sources was quite high with respect to duration of adjuvant hormonal therapy (never, <1 y, 1–4 y, and ≥5 y). For duration of use of any hormonal therapy, there was 85% agreement between our two assessments with a κ statistic of 0.79, and for duration of tamoxifen use, there was 86% agreement with a κ statistic of 0.80. In addition, detailed information was ascertained from both telephone interviews and medical record reviews on breast cancer surgeries, radiation therapy, chemotherapy, and treatment with trastuzamab.

Our primary outcomes of interest were ER+, ER+/progesterone receptor (PR)+, ER−, and ER−/PR− second primary contralateral breast cancer. Data on the ER and PR status of these second tumors were obtained from two sources, our medical record reviews and CSS (which has routinely recorded data on ER status of all breast cancer patients since 1988). Data on ER and PR status from one or both of these sources was obtained for 97% of all cases, and for the 333 cases with data from both sources, ER status were discordant for only 3 cases (1%) and PR status was discordant for only 6 cases (2%). In these cases, data from our medical record review were given priority because of the careful and detailed search for data on ER and PR status we conducted.

Associations between use of adjuvant hormonal therapy, and tamoxifen specifically, and risk of ER+ and ER− second primary contralateral breast cancer were estimated using conditional logistic regression. Conditional logistic regression was used because of the individual matching of controls to cases on four factors used in our nested case-control study design, and so all models were implicitly adjusted for each of the matching variables (age, diagnosis year, county, and race). Odds ratios (OR) and 95% confidence intervals (CI) were calculated as estimates of the relative risk. All statistical tests were two sided. We systematically assessed a series of potential confounders including established breast cancer risk factors, other breast cancer treatments, and tumor characteristics (listed in Table 1). Only radiation therapy for first breast cancer changed our risk estimates by >10% when adjusted for in the statistical model, and so our final risk estimates were only additionally adjusted for this variable. All analyses were conducted using Stata SE. Our sample size precluded meaningful assessments of the influence of potential effect modifiers, such as age, BMI, and the interval between first breast cancer diagnosis and reference date, on the relationships between adjuvant hormonal therapies and risk of different subtypes of contralateral breast cancer defined by hormone receptor status.

Table 2. Use of adjuvant hormonal therapy and risk of second primary contralateral breast cancer by hormone receptor status

Use of adjuvant hormonal therapy	Controls (*n* = 727)	Contralateral cases (*n* = 367)	OR* (95% CI)
	n (%)	*n* (%)	
All contralateral cases			
Never	218 (30.0)	144 (39.2)	1.0 (Reference)
Ever	509 (70.0)	223 (60.8)	0.6 (0.5–0.8)
<1 y	99 (13.6)	50 (13.6)	0.7 (0.5–1.1)
1–4 y	276 (40.0)	118 (32.2)	0.6 (0.4–0.8)
≥5 y	134 (18.4)	55 (15.0)	0.5 (0.3–0.8)
ER+ contralateral cases			
Never	182 (30.5)	132 (43.6)	1.0 (Reference)
Ever	415 (69.5)	171 (56.4)	0.5 (0.4–0.7)
<1 y	71 (12.7)	39 (12.9)	0.7 (0.4–1.1)
1–4 y	216 (38.7)	94 (31.0)	0.5 (0.4–0.7)
≥5 y	104 (18.6)	38 (12.5)	0.4 (0.2–0.6)
ER+/PR+ contralateral cases			
Never	151 (33.1)	111 (47.8)	1.0 (Reference)
Ever	305 (66.9)	121 (52.2)	0.5 (0.3–0.7)
<1 y	56 (12.3)	33 (14.2)	0.8 (0.4–1.3)
1–4 y	174 (38.2)	62 (26.7)	0.4 (0.3–0.7)
≥5 y	74 (16.3)	26 (11.2)	0.4 (0.2–0.7)
ER− contralateral cases			
Never	29 (27.1)	10 (19.2)	1.0 (Reference)
Ever	78 (72.9)	42 (80.8)	1.3 (0.6–3.0)
<1 y	16 (15.0)	9 (17.3)	1.3 (0.4–4.3)
1–4 y	43 (40.2)	17 (32.7)	1.0 (0.4–2.4)
≥5 y	19 (17.8)	16 (30.8)	3.8 (0.98–14.6)
ER−/PR− contralateral cases			
Never	27 (29.7)	9 (20.0)	1.0 (Reference)
Ever	64 (10.3)	36 (80.0)	1.4 (0.6–3.3)
<1 y	14 (15.4)	7 (15.6)	1.0 (0.3–3.6)
1–4 y	37 (40.7)	16 (35.6)	1.1 (0.4–3.0)
≥5 y	13 (14.3)	13 (28.9)	4.9 (1.1–22.5)

NOTE: The 12 cases with missing ER status and their matched 23 matched controls were excluded from the ER-specific analyses, and the 90 cases with other/missing ER/PR status and their matched 180 matched controls were excluded from the ER/PR-specific analyses.
*ORs and 95% CIs were estimated using conditional logistic regression and are adjusted for radiation therapy.

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Table 3. Use of tamoxifen and risk of second primary contralateral breast cancer by hormone receptor status

Use of tamoxifen	Controls (n = 674)	Contralateral cases (n = 358)	OR* (95% CI)
	n (%)	n (%)	
All contralateral cases			
Never	212 (31.4)	144 (40.2)	1.0 (Reference)
Ever	462 (68.6)	214 (59.8)	0.6 (0.5–0.8)
<1 y	86 (12.8)	48 (13.4)	0.8 (0.5–1.2)
1–4 y	258 (38.3)	113 (31.6)	0.6 (0.4–0.8)
≥5 y	115 (17.1)	51 (14.2)	0.6 (0.4–0.8)
ER+ contralateral cases			
Never	178 (32.0)	132 (44.8)	1.0 (Reference)
Ever	378 (68.0)	165 (55.2)	0.5 (0.4–0.7)
<1 y	65 (11.6)	37 (12.5)	0.7 (0.4–1.2)
1–4 y	209 (37.6)	90 (30.3)	0.5 (0.4–0.8)
≥5 y	98 (17.6)	36 (12.1)	0.4 (0.3–0.7)
ER+/PR+ contralateral cases			
Never	149 (34.9)	111 (48.7)	1.0 (Reference)
Ever	278 (65.1)	117 (51.3)	0.5 (0.4–0.7)
<1 y	52 (12.2)	32 (14.0)	0.7 (0.4–1.3)
1–4 y	155 (36.3)	58 (25.4)	0.5 (0.3–0.7)
≥5 y	66 (15.5)	25 (11.0)	0.5 (0.3–0.8)
ER− contralateral cases			
Never	27 (27.8)	10 (20.0)	1.0 (Reference)
Ever	70 (72.2)	40 (80.0)	1.6 (0.7–3.3)
<1 y	16 (16.5)	10 (20.0)	1.1 (0.3–3.8)
1–4 y	40 (41.2)	16 (32.0)	0.7 (0.3–1.9)
≥5 y	14 (14.4)	14 (28.0)	4.4 (1.03–19.0)
ER−/PR− contralateral cases			
Never	25 (30.5)	10 (22.7)	1.0 (Reference)
Ever	57 (69.5)	34 (77.3)	1.2 (0.5–2.9)
<1 y	14 (17.0)	8 (18.2)	0.9 (0.3–3.2)
1–4 y	34 (41.5)	15 (34.1)	0.8 (0.3–2.2)
≥5 y	9 (11.0)	11 (25.0)	5.9 (1.1–32.6)

NOTE: Ever users of other forms of adjuvant hormonal therapy were excluded from all analyses presented in this table. The 11 cases with missing ER status and their matched 23 matched controls were excluded from the ER-specific analyses, and the 90 cases with other/missing ER/PR status and their matched 180 matched controls were excluded from the ER/PR-specific analyses.

* ORs and 95% CIs were estimated using conditional logistic regression and are adjusted for radiation therapy.

Results

Nearly equal proportions of cases and controls received radiation therapy and chemotherapy for their first primary breast cancer (Table 1). The first breast cancers diagnosed among cases were somewhat more likely to be stage II or III and >2.0 cm in size compared with those diagnosed among controls. Cases were also somewhat more likely to have a first-degree family history of breast cancer and to be obese (have a BMI of ≥30.0 kg/m^2) at both first breast cancer diagnosis and reference date.

Overall, ever users of any type of adjuvant hormonal therapy and tamoxifen specifically had reduced risks of second primary contralateral breast cancer (OR, 0.6; 95% CI, 0.5–0.8; and OR, 0.6; 95% CI, 0.5–0.8, respectively; Tables 2 and 3). These reductions in risk were confined to users of these therapies for 1 year or longer. They were also confined to reductions in risk of hormone receptor–positive contralateral tumors. Also, ever use of any type of adjuvant hormonal therapy, and use of tamoxifen specifically, was not associated with an altered risk of ER− or ER−/PR− contralateral breast cancer.

Use of adjuvant hormonal therapy or tamoxifen for 5 years or longer was associated with reduced risks of ER+ (OR, 0.4; 95% CI, 0.2–0.6; and OR, 0.4; 95% CI, 0.3–0.7, respectively) and ER+/PR+ (OR, 0.4; 95% CI, 0.2–0.7; and OR, 0.5; 95% CI, 0.3–0.8, respectively) contralateral breast cancers. In contrast, use of adjuvant hormonal therapy or tamoxifen for 5 years or longer substantially elevated risks of ER− (OR, 3.8; 95% CI, 1.0–14.6; and OR, 4.4; 95% CI, 1.0–19.0, respectively) and ER−/PR− (OR, 4.9; 95% CI, 1.1–22.5; and OR, 5.9; 95% CI, 1.1–32.6, respectively) contralateral tumors.

Discussion

It is well-established that adjuvant hormonal therapy in general and tamoxifen in particular reduce the risk of contralateral breast cancer among women diagnosed with hormone receptor–positive breast cancer (2). In this study, we confirmed the benefit of this treatment with respect to reducing risk of contralateral breast cancer overall, and hormone receptor–positive contralateral disease in particular. However, we also observed that women with

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first primary ER+ breast cancer treated with 5 years of tamoxifen have a 4.4-fold increased risk of developing an ER− second primary contralateral breast cancer and a 5.9-fold increased risk of developing an ER−/PR− contralateral tumor. This finding is consistent with our prior report based on SEER data, which observed that use of tamoxifen was associated with a 4.9-fold increased risk of ER− contralateral breast cancer (7). However, our prior study had certain design limitations given that it was based only on cancer registry data and could not evaluate duration of tamoxifen use. Our results are also consistent with the observation in several primarily institutional-based series that the proportion of contralateral tumors that are ER− is substantially higher in women who used adjuvant tamoxifen compared with those who did not (8–11). Major strengths of this study, which was designed specifically to evaluate this association, include the collection of detailed data on use of adjuvant hormonal therapy and a variety of other potentially relevant exposures through in-depth telephone interviews and medical record reviews, the ability to assess the impact of duration of adjuvant hormonal therapy use, and incorporation of multivariate adjusted statistical modeling.

Our primary hypothesis to explain this association is based on tamoxifen's mechanism of action. Tamoxifen suppresses the activity of ER+ breast cancer cells through competitive inhibition of the ER. However, ER expression is heterogeneous in most breast cancers, so whereas the majority of cancer cells in ER+ breast cancer express ER, some will not (3). Consequently, prolonged treatment with tamoxifen could provide a competitive advantage for the growth of ER− breast cancer cells. Such an effect has been documented with respect to breast cancer recurrences. One study observed that although recurrent tumors express comparable levels of ER as primary tumors among nonusers of tamoxifen, recurrences among tamoxifen users express less ER compared with the primary tumor (4). It should be noted though that we did not observe a dose-response relationship between duration of hormonal therapy and risk of ER− contralateral breast cancer, rather the increased risk observed was confined to users for 5 years or longer. The reasons for this are unclear, it could be that a threshold effect is present and that a certain length of exposure is needed to foster an environment that promotes ER− tumor growth. Alternatively, it could simply be that our study lacked sufficient statistical power to adequately address a dose-response relationship for the relatively rare outcome of an ER− second primary contralateral tumor.

A potential limitation of this study is recall bias since participants were asked to recall exposures that for some could have occurred up to 15 years in the past. However, this bias was limited through the conduct of medical record reviews where information on adjuvant hormonal therapy was obtained for 94% of participants. In addition, the agreement between self-reported interview history of adjuvant hormonal therapy and data abstracted from medical records was quite high with 85% agreement and a κ value of 0.79. Another limitation of this study was its sample size given that ER− and ER−/PR− contralateral breast cancers are relatively rare outcomes. However, given the magnitude of the association between adjuvant hormonal therapy and risk of these types of contralateral breast cancer, our sample size was sufficient to detect statistically significant relationships. With respect to the generalizability of this study, it is important to note that almost all users of adjuvant hormonal therapy in this study used tamoxifen, so use of other types of hormonal therapy, such as aromatase inhibitors, could not be assessed separately. Thus, the extent to which use of aromatase inhibitors may also increase risk of ER− contralateral breast cancer remains unknown. However, given the potential mechanism through which tamoxifen could enhance the growth of ER− contralateral tumors, one could reasonably hypothesize that aromatase inhibitors would have a similar impact on risk.

The considerable benefits of adjuvant hormonal therapy for women with hormone receptor–positive breast cancer are clear as they confer substantially reduced risks of breast cancer recurrence, contralateral breast cancer, and mortality. Nevertheless, risk of a hormone receptor–negative contralateral breast cancer may now need to be tallied among the risks of treatment with tamoxifen, and further studies are needed to determine if other hormonal therapies and the increasingly used aromatase inhibitors in particular, also carry this risk. Development of ER− and ER−/PR− disease is of particular clinical concern given the substantially poorer prognosis associated with these tumors compared with ER+ disease. Specifically, women with ER−/PR− breast cancer are 2.3-fold more likely to die of their disease than are women with ER+/PR+ breast cancer (12).

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Correction: Adjuvant Hormonal Therapy for Breast Cancer and Risk of Hormone Receptor-Specific Subtypes of Contralateral Breast Cancer

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1. Li CI, Daling JR, Porter PL, Tang M-TC, Malone KE. Adjuvant hormonal therapy for breast cancer and risk of hormone receptor-specific subtypes of contralateral breast cancer. Cancer Res 2009; 69:6865–70.

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Adjuvant Hormonal Therapy for Breast Cancer and Risk of Hormone Receptor–Specific Subtypes of Contralateral Breast Cancer

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