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

Christopher I. Li¹, Janet R. Daling¹, Peggy L. Porter^{1,2}, Mei-Tzu C. Tang¹, and Kathleen E. Malone¹

¹ Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA

² Division of Human Biology, Fred Hutchinson Cancer Research Center, Seattle, WA

Abstract

Compared to 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 records 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 to 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 to 0.7], but a 4.4-fold (95% CI: 1.03 to 19.0) increased risk of ER– contralateral breast cancer. Tamoxifen use for < 5 years was not associated with ER– contralateral breast cancer risk. While 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 to ER+ tumors.

Keywords

Breast cancer; tamoxifen; estrogen receptor; progesterone receptor; contralateral breast cancer

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

Corresponding author: Christopher I. Li, MD, PhD, Fred Hutchinson Cancer Research Center, 1100 Fairview Ave. N., M4-C308, P.O. Box 19024, Seattle, WA 98109-1024, Telephone: 206.667.7444, Fax: 206.667.5948, E-mail: cili@fhcrc.org.

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mortality. A meta-analysis of 55 of these trials indicates that use of tamoxifen for five years reduces the risk of contralateral breast cancer by 47%.(2) While adjuvant tamoxifen unequivocally reduces subsequent risk of estrogen receptor positive (ER+) contralateral breast cancer, it is possible that it may also increase the risk of estrogen receptor negative (ER-) disease. Given the heterogeneous nature of ER expression in breast tumors,(3) it is plausible that while 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 estrogen receptor negative (ER-) contralateral breast cancer. Specifically, compared to non-users, 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 (NSABP) 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 to only 11% of those diagnosed among nonusers of tamoxifen.(8) Similarly, three institution based series conducted in Detroit, Michigan (n=144 contralateral cases),(9) Houston, Texas (n=193 contralateral cases),(10) and the Netherlands (n=150 contralateral cases)(11) all found that the proportion of ER- contralateral tumors diagnosed among tamoxifen users was higher than that among nonusers of tamoxifen (55% vs. 10% in the Detroit study; 53% vs. 12% in the Houston study; and 37% vs. 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 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.

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 years 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 approximately 99% of all incident cancer cases diagnosed in CSS's catchment area are ascertained. Women with stage IIIB 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 years of age were excluded because adjuvant hormonal therapy is not always recommended for premenopausal women, and women ≥ 80 years of age were excluded in order 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 in order to overcome the bias that would have resulted from excluding potentially eligible participants who died prior to 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 six months 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 vs. 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 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.

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, lifestyle factors, anthropometric characteristics, and breast cancer treatments they received. Women were asked to recall their exposures prior to 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, body mass index (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 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 was viewed to have a higher validity considering the advanced age of many participants at study contact and that many were required to recall exposures more than 10 years 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 year, 1–4 years, and ≥ 5 years). For duration of use of any hormonal therapy there was 85% agreement between our two assessments with a kappa statistic of 0.79, and for duration of tamoxifen use there was 86% agreement with a kappa 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 trastuzumab.

Our primary outcomes of interest were ER+, ER+/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 employed 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 (ORs) and 95% confidence intervals (CIs) 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 greater than 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 (College Station, TX). Our sample size precluded meaningful assessments of the influence of potential effect modifiers, such as age, body mass index, 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.

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 IIIA and >2.0 cm in size compared to 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 body mass index ≥ 30.0 kg/m²) 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) (Table 2 and Table 3). These reductions in risk were confined to users of these therapies for one 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 first primary ER+ breast cancer treated with five 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 to 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 estrogen receptor positive breast cancer cells through competitive inhibition of the estrogen receptor. However, ER expression is heterogeneous in most breast cancers so while 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 while 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 five 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 a 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 kappa 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 to 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)

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Table 1
Characteristics of controls and contralateral breast cancer cases

Characteristic	Controls (n=727)		Contralateral Cases (n=367)	
	n	%	n	%
<i>Demographic characteristics</i>				
Age at first breast cancer diagnosis, yrs				
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), yrs				
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	
<i>Treatments for first primary breast cancer</i>				
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	

Characteristic	Controls (n=727)		Contralateral Cases (n=367)	
	n	%	n	%
<i>Tumor characteristics</i>				
AJCC stage				
I	495	68.1	239	65.1
II, IIIA, or IIIB	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	
<i>Patient characteristics</i>				
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	
Number 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	
Body mass index at first breast cancer diagnosis, kg/m²				
<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	
Body mass index at reference date, kg/m²				
<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	

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	ref
Ever	509	70.0	223	60.8	0.6	0.5–0.8
<1 year	99	13.6	50	13.6	0.7	0.5–1.1
1–4 years	276	40.0	118	32.2	0.6	0.4–0.8
≥5 years	134	18.4	55	15.0	0.5	0.3–0.8
ER+ contralateral cases						
Never	182	30.5	132	43.6	1.0	ref
Ever	415	69.5	171	56.4	0.5	0.4–0.7
<1 year	71	12.7	39	12.9	0.7	0.4–1.1
1–4 years	216	38.7	94	31.0	0.5	0.4–0.7
≥5 years	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	ref
Ever	305	66.9	121	52.2	0.5	0.3–0.7
<1 year	56	12.3	33	14.2	0.8	0.4–1.3
1–4 years	174	38.2	62	26.7	0.4	0.3–0.7
≥5 years	74	16.3	26	11.2	0.4	0.2–0.7
ER– contralateral cases						
Never	29	27.1	10	19.2	1.0	ref
Ever	78	72.9	42	80.8	1.3	0.6–3.0
<1 year	16	15.0	9	17.3	1.3	0.4–4.3
1–4 years	43	40.2	17	32.7	1.0	0.4–2.4
≥5 years	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	ref

Use of Adjuvant Hormonal Therapy	Controls (n=727)		Contralateral Cases (n=367)		OR [*]	95% CI
	n	%	n	%		
Ever	64	10.3	36	80.0	1.4	0.6–3.3
<1 year	14	15.4	7	15.6	1.0	0.3–3.6
1–4 years	37	40.7	16	35.6	1.1	0.4–3.0
≥5 years	13	14.3	13	28.9	4.9	1.1–22.5

^{*} Odds ratios (OR) and 95% confidence intervals (CI) were estimated using conditional logistic regression and are adjusted for radiation therapy.

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.

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	ref	
Ever	462	68.6	214	59.8	0.6	0.5–0.8	
<1 year	86	12.8	48	13.4	0.8	0.5–1.2	
1–4 years	258	38.3	113	31.6	0.6	0.4–0.8	
≥5 years	115	17.1	51	14.2	0.6	0.4–0.8	
ER+ contralateral cases							
Never	178	32.0	132	44.8	1.0	ref	
Ever	378	68.0	165	55.2	0.5	0.4–0.7	
<1 year	65	11.6	37	12.5	0.7	0.4–1.2	
1–4 years	209	37.6	90	30.3	0.5	0.4–0.8	
≥5 years	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	ref	
Ever	278	65.1	117	51.3	0.5	0.4–0.7	
<1 year	52	12.2	32	14.0	0.7	0.4–1.3	
1–4 years	155	36.3	58	25.4	0.5	0.3–0.7	
≥5 years	66	15.5	25	11.0	0.5	0.3–0.8	
ER– contralateral cases							
Never	27	27.8	10	20.0	1.0	ref	
Ever	70	72.2	40	80.0	1.6	0.7–3.3	
<1 year	16	16.5	10	20.0	1.1	0.3–3.8	
1–4 years	40	41.2	16	32.0	0.7	0.3–1.9	
≥5 years	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	ref	

Use of Tamoxifen	Controls (n=674)		Contralateral Cases (n=358)		OR	95% CI
	n	%	n	%		
Ever	57	69.5	34	77.3	1.2	0.5-2.9
<1 year	14	17.0	8	18.2	0.9	0.3-3.2
1-4 years	34	41.5	15	34.1	0.8	0.3-2.2
≥5 years	9	11.0	11	25.0	5.9	1.1-32.6

* Odds ratios (OR) and 95% confidence intervals (CI) were estimated using conditional logistic regression and are adjusted for radiation therapy. Ever users of other forms of adjuvant hormonal therapy were excluded from all analyses presented in this table.

Note: 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.