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Duration of Tamoxifen Use and the Risk of Contralateral Breast Cancer in BRCA1 and BRCA2 Mutation Carriers

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Abstract

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Purpose—Women with a mutation in BRCA1 or BRCA2 face a lifetime risk of breast cancer of approximately 80%. Tamoxifen treatment of the first cancer has been associated with a reduction in the risk of a subsequent contralateral cancer.

Methods—We studied 1504 women with a known BRCA1 or BRCA2 mutation, 411 women with bilateral breast cancer (cases) and 1093 women with unilateral breast cancer (controls) in a matched case-control study. Control women were of similar age and had a similar age of diagnosis of first breast cancer as the cases. For each woman who used tamoxifen, the starting and stopping dates were abstracted and the duration of tamoxifen use was calculated.

Results—331 women had used tamoxifen (22%); of these 84 (25%) had completed four or more years of tamoxifen, the remainder stopped prematurely or were current users. For women with up to one year of tamoxifen use, the odds ratio for contralateral breast cancer was 0.37 (95% CI: 0.20 – 0.69; $p = 0.001$) compared to women with no tamoxifen use. Among women with one to four years of tamoxifen use the odds ratio was 0.53 (95% CI: 0.32-0.87; $p = 0.01$). Among women with four or more years of tamoxifen use the odds ratio was 0.83 (95% CI: 0.44 -1.55; $p = 0.55$).

Conclusion—Short-term use of tamoxifen for chemoprevention in BRCA1 and BRCA2 mutation carriers may be as effective as a conventional five year course of treatment.

Keywords

Breast cancer; tamoxifen; oophorectomy; BRCA1; BRCA2

Introduction

The lifetime risk of breast cancer in a woman who carries a deleterious mutation in BRCA1 or BRCA2 is approximately 80% [1] and following an initial diagnosis of breast cancer the annual risk of contralateral breast cancer is approximately 3% [2]. Tamoxifen has been shown to reduce the risk of contralateral breast cancer in carriers of BRCA1 or BRCA2 mutations [3-5], in particular among women with intact ovaries [4]. In 2006, in a case-control study of 285 bilateral cases and 751 unilateral controls, we reported a reduction in contralateral breast cancer risk of 50% associated with any tamoxifen use [4]. In that study, we did not see a trend in the degree of protection with duration of tamoxifen use up to five years, but the estimates were imprecise. We have observed that a high proportion of women in this cohort stopped using tamoxifen prior to completion of the recommended five-year course [6] and it is important to understand if non-compliance impacts on the risk of second primary breast cancer. We continue to accrue study subjects to our international BRCA carrier registry and the current manuscript addresses the question of tamoxifen protection associated with duration of use.

Methods

Study Subjects

Information on women with hereditary breast cancer was submitted to the study center at the Womens College Research Institute in Toronto by investigators at each of 51 contributing centers in ten countries. These centers were requested to complete data forms for all known cases of female breast cancer, unilateral or bilateral, carrying a verified BRCA1 or BRCA2

mutation. The institutional review boards of the host approved the study. All subjects provided written informed consent. The majority of these cases were identified through genetic counseling and risk assessment programs offered to women from high-risk families. The data center received information on a total of 5,984 cases of invasive breast cancer in carriers of pathogenic BRCA1 or BRCA2 mutations. Patients were excluded from the current study if the first cancer was diagnosed prior to January 1, 1970 (i.e. before tamoxifen was in use (n = 161). Women with ovarian cancer diagnosed at any time prior to the contralateral breast cancer were excluded (n = 534). Synchronous bilateral cases were excluded because there would be no opportunity for the patient to take tamoxifen prior to the onset of the contralateral cancer (n = 145). Similarly, women with bilateral mastectomy were excluded because these were not at risk for contralateral breast cancer (n= 975). Women with an oophorectomy were excluded because we wished to dissociate the protective effect of oophorectomy from that of tamoxifen (n = 821). In addition, we excluded 676 women because data was missing on tamoxifen use or on another key variable.

After these exclusions, there were 2,672 women with breast cancer available for study, including 542 women with bilateral breast cancer (potential cases) and 2130 women with unilateral breast cancer (potential controls). Controls were selected to be born within three years of the birth date of the matched case, and to have been diagnosed with breast cancer at an age within two years of the age of the first diagnosis of breast cancer of the case. Cases and controls were carriers of a mutation in the same gene (BRCA1 or BRCA2) and regional residence (North America, Poland, other country). Each control was followed for a period at least as long as the follow-up period of the matched case. For each bilateral case, we attempted to identify one or more unilateral control patients. No woman received tamoxifen prior to the diagnosis of the initial breast cancer. All of the exposures in cases and controls were defined for the time period equivalent to the period between the first diagnosis and the contralateral cancer of the matched case. For each woman who reported use of tamoxifen, we evaluated the duration of tamoxifen from the date of first use to the date of last use. If the bilateral case developed contralateral breast cancer within five years of the initiation of tamoxifen, then the use of tamoxifen in the matched control was truncated at the date of diagnosis in the case.

Because of the requirement for genetic testing of the 2,672 study subjects (which is available to living women) these subjects represent prevalent cases; the median year of diagnosis of the first breast cancer was 1996 (range 1970 to 2013). Our study was restricted to living subjects, because it was only possible to perform mutation analysis on living women, and because risk factor information was obtained by questionnaire. The questionnaires were completed between the years 1980 and 2013, on average 7.2 years after the diagnosis of the first case. BRCA1 and BRCA2 mutation analysis was performed using several established detection techniques, and all mutations were confirmed by direct sequencing of DNA samples.

Study Protocol

Case and control women completed a questionnaire which asked about the medical and surgical treatment of the initial breast cancer. In some centers the questionnaire was

administered by telephone interview. The years of diagnosis of the initial and contralateral breast cancer were recorded. Women were asked if they had received adjuvant tamoxifen as a treatment for the first breast cancer, and if so, the dose, dates and duration of tamoxifen treatment. Women were also asked to report on the type of surgical treatment they received (lumpectomy, unilateral mastectomy, or bilateral mastectomy). Women were asked if they had undergone bilateral oophorectomy, either prior to cancer diagnosis or thereafter. Women were asked about chemotherapy (yes/no) and radiotherapy (yes/no) as treatment of the initial breast cancer. Additional variables of interest included smoking, reproductive history, and ethnicity.

Statistical Analysis

A matched case-control analysis was performed. The frequency of tamoxifen use was compared between the bilateral cases and unilateral matched controls. The univariate odds ratios (and p-values) for contralateral breast cancer associated with tamoxifen use were calculated using conditional logistic regression. The odds ratios for contralateral breast cancer associated with tamoxifen use were adjusted for other treatments received (radiotherapy and chemotherapy). Duration of tamoxifen use was defined as follows: up to one year of use, one to four years of use and four or more years of use. We estimated the relative risk reduction of tamoxifen separately for BRCA1 and BRCA2 mutation carriers and as a function of duration of exposure. We also performed a sub-analysis wherein cases were restricted to those diagnosed with contralateral breast cancer a minimum of four years after the initial diagnosis. This was done in order to dissociate the period of (short-term) tamoxifen use from the period of risk for contralateral breast cancer (i.e., to ensure that no woman was taking tamoxifen at the time of diagnosis of contralateral breast cancer or during the year before). All calculations were performed using the SAS Statistical Package.

Results

Tamoxifen use was reported by 14.8% of the bilateral cases and by 24.7% of the unilateral controls ($p = 0.0001$). The characteristics of the 411 cases of bilateral breast cancer and 1093 cases of unilateral cancer are presented in Table 1. The univariate odds ratio for tamoxifen use and contralateral breast cancer (both genes combined) was 0.52 (95% CI: 0.37 to 0.73) and the adjusted odds ratio (controlling for radiotherapy and chemotherapy) was 0.53 (95% CI: 0.37 to 0.75) ($p = 0.003$) (Table 2).

The protective effect of tamoxifen was similar for BRCA1 and BRCA2 mutation carriers; among the BRCA1 cases and matched controls, the univariate odds ratio was 0.58 (95% CI: 0.39 to 0.86) and among the BRCA2 mutation carriers, the odds ratio was 0.36 (95% CI: 0.17 to 0.75). The adjusted odds ratio was 0.58 (95% CI: 0.39 to 0.85) for BRCA1 mutation carriers and was 0.39 (95% CI: 0.19 to 0.83) for BRCA2 mutation carriers.

There was no trend of increasing protection against contralateral breast cancer with increasing duration of tamoxifen use - in fact, the strongest protective effect was observed for women with less than one year of use (Table 2). Among women with up to one year of tamoxifen use (either mutation) the odds ratio for contralateral breast cancer was 0.37 (95% CI: 0.20 to 0.67; $p = 0.001$); among women with one to four years of tamoxifen use the odds

ratio was 0.53 (95% CI: 0.32 to 0.87; $p = 0.01$); among women with four or more years of tamoxifen use the odds ratio was 0.83 (95% 0.44 to 1.55; $p = 0.55$). We performed a separate analysis of short-term tamoxifen (one year or less) restricting cases to those women who experienced a contralateral breast cancer four or more years after the diagnosis of the initial cancer (and their matched controls). In this analysis, a minimum of two years had elapsed between the date of last tamoxifen use and the date of contralateral cancer. On average, in this subgroup, the contralateral cancer was diagnosed 7.4 years after the initial diagnosis (range 4 to 26 years). The protective effect of short-term tamoxifen use persisted in this subgroup well after tamoxifen was terminated (Table 3).

We excluded women who had undergone an oophorectomy, but not those who experienced natural menopause. Similar risk reductions were observed with tamoxifen among those women who were diagnosed with second primary cancer when post-menopausal and when they were pre-menopausal (Table 4).

Discussion

We observed that the risk of contralateral breast cancer was reduced by approximately 50% in carriers of BRCA1 and BRCA2 mutations when tamoxifen was given as adjuvant treatment for the initial breast cancer. Adjusting for the effects of chemotherapy and radiotherapy did not materially alter this estimate. This association has been reported before [3-5] - what is novel in the present study is that the observed protective effect was equal to or greater for women who used tamoxifen for a short time (less than one year) than for women who completed the recommended course (four or more years). Our data does not imply that the recommended course of tamoxifen should be shortened -the primary goals of tamoxifen treatment are to reduce the risks of local and distant recurrence, and prevention of contralateral breast cancer is a secondary, albeit important goal. The present study does not address the relationship between short-course tamoxifen and these other clinical endpoints. Many hereditary breast cancer patients (excluded here) undergo bilateral mastectomies and for them the occurrence of contralateral breast cancer is not relevant; for them the goal of tamoxifen is to prevent distant recurrence. Furthermore, we excluded women who have undergone oophorectomy and this should be a topic of future study.

These results may however, be relevant for women considering primary prevention. If the odds ratio associated with a second primary breast cancer and one year of tamoxifen were to be the same as that for primary breast cancer, this would provide a compelling rationale for women with a BRCA1 or BRCA2 mutation who have not had a preventive mastectomy or oophorectomy to consider short-term tamoxifen. At present, tamoxifen is the only approved drug for breast cancer prevention in pre-menopausal women (in post-menopausal women raloxifene [7] and exemestane [8] and anastrozole [9] may also be considered). Many women are reluctant to take tamoxifen because of a fear of side effects [9]. In this respect, a short course of tamoxifen might be preferred over the recommended five year course. Side effects of tamoxifen include thromboembolism and endometrial cancer. Iqbal et al recently performed a meta-analysis of these side effects, based on data from the randomized trials [11] and concluded that the risks of these serious conditions were less than one per thousand per year and that the risks did not persist beyond the period of active treatment. The results

of the present study confirm our earlier reports [3, 4] and that of others [5]. In a historical cohort study of 1583 *BRCA1* and 861 *BRCA2* mutation carriers, the adjusted hazard ratios for second primary breast cancers associated with any tamoxifen use were 0.38 (95% CI: 0.27-0.55) for *BRCA1* mutation carriers and 0.33 (95% CI 0.22-0.50) for *BRCA2* mutation carriers [5].

The precise mechanism(s) of action whereby tamoxifen prevents breast cancer is (are) not clear. If activity were directed to established tumors only, then we would expect to see a specificity for ER-positive cancers. This appears to be true for cancer in the general population [12-13], but for *BRCA1*-associated cancers, the majority of cancers are ER-negative [14]. Traditionally, tamoxifen has been thought of as cytostatic (and not cytotoxic). But if we consider that a proportion of ER-positive cancers will regress spontaneously when hormone exposure is withdrawn (reviewed in ref 15), then there is the possibility that ER-receptor blockade could also prompt some tumors to regress. The long duration of the protective effect of tamoxifen supports a mechanism that persists beyond that of stalling the growth of established tumors and prompts the question of whether tamoxifen also acts in earlier stages of cancer development [16]. It has been proposed that anti-hormonal therapy will reduce the number of cancer precursor cells [17-19], and thereby potentially impart a long-term protective effect. An alternate possibility is that tamoxifen induces stromal changes in the normal breast that renders it less tumorigenic (an example of this might be the salutary effect of tamoxifen on mammographic density [20]).

There are several limitations to our study. The interview took place on average, two years after the diagnosis of the second cancer and seven years after the diagnosis of the first cancer. It is unlikely that women would not accurately recall if they had ever used tamoxifen, but they may not recall the exact duration of use. It is possible that women who survived for this amount of time may not be completely representative of the hereditary breast cancer population at large. We excluded women who had undergone an oophorectomy because we wished to study the effect of tamoxifen in women who were producing ovarian hormones. We did not have information on estrogen receptor status for the majority of the patients in this study and therefore we were not able to subdivide the sample into ER-positive and ER-negative patients. Presumably the majority of patients who were treated with tamoxifen had an ER-positive cancer. Among this subgroup, the majority of the second primary cancers are expected to be ER-negative [21] and therefore it is unlikely that reductions of the magnitude observed here can be generated purely through the prevention of ER-positive cancers. We do not know the reason why women stopped tamoxifen early. In our earlier study, tamoxifen did not appear to be effective in women who have experienced surgical menopause [4], but among women who have passed natural menopause (and who have circulating estrogens derived from aromatisation of ovarian androgens) the drug appears to be beneficial.

It is premature to conclude that the degree of prevention for primary and secondary prevention are the same but it is reassuring that, in this and the other large study conducted to date [5], the protective effects on contralateral cancer are similar (and large). The recommended duration of tamoxifen for chemoprevention is based on data on contralateral breast cancers among women who were treated for primary breast cancers [11-13, 22, 23]. It

is not necessarily the case that the optimum duration of tamoxifen for the treatment and for chemoprevention be the same. Shorter durations have been proposed [24], but have not been studied. Based on the rarity of serious side effects [10] and the potential benefit described here, and elsewhere [5], we believe that a randomized trial of one year of tamoxifen versus placebo in BRCA1 and BRCA2 mutation carriers is feasible.

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References

1. Ford D, Easton DF, Stratton M, et al. Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families. *Am J Hum Genet.* 1998; 62:676–89. [PubMed: 9497246]
2. Metcalfe K, Gershman S, Lynch HT, et al. Predictors of contralateral breast cancer in BRCA1 and BRCA2 mutation carriers. *Br J Cancer.* 2011; 104:1384–92. [PubMed: 21487411]
3. Narod SA, Brunet JS, Ghadirian P, et al. Tamoxifen and risk of contralateral breast cancer in BRCA1 and BRCA2 mutation carriers: a case-control study. Hereditary Breast Cancer Clinical Study Group. *Lancet.* 2000; 356:1876–81. [PubMed: 11130383]
4. Gronwald J, Tung N, Foulkes WD, et al. Hereditary Breast Cancer Clinical Study Group. Tamoxifen and contralateral breast cancer in BRCA1 and BRCA2 carriers: an update. *Int J Cancer.* 2006; 118:2281–4. [PubMed: 16331614]
5. Phillips K, Milne RL, Rookus MA, et al. Tamoxifen and risk of contralateral breast cancer for BRCA1 and BRCA2 mutation carriers. *J Clin Oncol.* 2013; 31:3091–9. [PubMed: 23918944]
6. Narod SA. Compliance with tamoxifen in women with breast cancer and a BRCA1 or BRCA2 mutation. *J Clin Oncol.* 2010; 28:e698–9. [PubMed: 20921464]
7. Vogel VG, Costantino JP, Wickerham DL, et al. Update of the National Surgical Adjuvant Breast and Bowel Project Study of Tamoxifen and Raloxifene (STAR) P-2 Trial: Preventing Breast Cancer. *Cancer Prev Res (Phila).* 2010; 3:696–706. [PubMed: 20404000]
8. Goss PE, Ingle JN, Alés-Martínez JE, et al. Exemestane for breast-cancer prevention in postmenopausal women. *N Engl J Med.* 2011; 364:2381–91. [PubMed: 21639806]
9. Cuzick J, Sestak I, Forbes JF, et al. Anastrozole for prevention of breast cancer in high-risk postmenopausal women (IBIS-II): an international, double-blind, randomised placebo-controlled trial. *Lancet.* 2013; piiS0140-6736:62292–8.
10. Iqbal J, Ginsburg OM, Wijeratne TD, et al. Endometrial cancer and venous thromboembolism in women under age 50 who take tamoxifen for prevention of breast cancer: A systematic review. *Cancer Treat Rev.* 2011; 38:318–28. [PubMed: 21775065]
11. Metcalfe KA, Snyder C, Seidel J, Hanna D, Lynch HT, Narod S. The use of preventive measures among healthy women who carry a BRCA1 or BRCA2 mutation. *Fam Cancer.* 2005; 4:97–103. [PubMed: 15951959]
12. Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. *J Natl Cancer Inst.* 1998; 90:1371–88. [PubMed: 9747868]
13. Fisher B, Dignam J, Bryant J, et al. Five versus more than five years of tamoxifen therapy for breast cancer patients with negative lymph nodes and estrogen receptor-positive tumors. *J Natl Cancer Inst.* 1996; 88:1529–42. [PubMed: 8901851]

14. Cuzick J, Warwick J, Pinney E, et al. Tamoxifen-induced reduction in mammographic density and breast cancer risk reduction: a nested case-control study. *J Natl Cancer Inst.* 2011; 103:744–52. [PubMed: 21483019]
15. Foulkes WD, Metcalfe K, Sun P, et al. Estrogen receptor status in BRCA1- and BRCA2-related breast cancer: the influence of age, grade, and histological type. *Clin Cancer Res.* 2004; 10:2029–34. [PubMed: 15041722]
16. Narod SA. Hormone replacement therapy and the risk of breast cancer. *Nat Rev Clin Oncol.* 2011; 8:669–76. [PubMed: 21808267]
17. Euhus D, Bu D, Xian-Jin X, et al. Tamoxifen down-regulates Ets Oncogene family members ET4 and ET5 in benign breast tissue: implications for durable risk reduction. *Cancer Prevention Research.* in press.
18. Joshi PA, Jackson HW, Beristain AG, et al. Progesterone induces adult mammary stem cell expansion. *Nature.* 2010; 465:803–7. [PubMed: 20445538]
19. Schramek D, Leibbrandt A, Sigl V, et al. Osteoclast differentiation factor RANKL controls development of progestin-driven mammary cancer. *Nature.* 2010; 468:98–102. [PubMed: 20881962]
20. Asselin-Labat ML, Vaillant F, Sheridan JM, et al. Control of mammary stem cell function by steroid hormone signalling. *Nature.* 2010; 465:798–802. [PubMed: 20383121]
21. Cuzick J, Warwick J, Pinney E, et al. Tamoxifen-induced reduction in mammographic density and breast cancer risk reduction: a nested case-control study. *J Natl Cancer Inst.* 2011; 103:744–52. [PubMed: 21483019]
22. Weitzel JN, Robson M, Pasini B, et al. A comparison of bilateral breast cancers in BRCA carriers. *Cancer Epidemiol Biomarkers Prev.* 2005; 14:1534–8. [PubMed: 15941968]
23. Cuzick J, Forbes JF, Sestak I, et al. Long-term results of tamoxifen prophylaxis for breast cancer-96-month follow-up of the randomized IBIS-I trial. *International Breast Cancer Intervention Study I Investigators. J Natl Cancer Inst.* 2007; 99:272–82. [PubMed: 17312304]
24. DeCensi A, Guerrieri-Gonzaga A, Gandini S, et al. Prognostic significance of Ki-67 labeling index after short-term presurgical tamoxifen in women with ER-positive breast cancer. *Ann Oncol.* 2011; 22:582–7. [PubMed: 20716629]

Table 1
Comparison of bilateral and unilateral breast cancer cases

	Unilateral N = 1093	Bilateral N = 411	P
Mean age (range)	50.7 (29-77)	51.3 (28-76)	0.28
Year of birth (range)	1951.7 (1921-80)	1951.4 (1921-80)	0.75
Mean age of first breast cancer (range)	40.6 (26-63)	39.8 (24-63)	0.14
Mean age of second breast cancer (range)	NA	45.7 (26-71)	
Mutation			
BRCA1	83.5%	81.0%	Matched
BRCA2	16.5%	19.0%	
Menopausal status			
Premenopausal	585 (55.4%)	194 (48.9%)	0.03
Postmenopausal	472 (44.7%)	203 (51.1%)	
Place of residence			
Northern America	512	239	Matched
Poland	474	122	
Other	107	50	
Parity (mean)	2.1	2.0	0.65
Smoke (ever)	46.7%	43.0%	0.19
Chemotherapy	80.7%	63.0%	0.0001
Radiotherapy	54.8%	52.3%	0.38
Tamoxifen			
Ever	24.7%	14.8%	0.0001
Mean use,(years)	0.69	0.44	0.007
Mean use, users (years)	2.5	3.0	0.15

^a: The data of controls in comparison are mean of means of each set

Table 2
Association between tamoxifen use and contralateral breast cancer by duration of use and by mutation

Mutation	Tamoxifen use (years)	Number of Tamoxifen users Bilateral/Unilateral		
			Odds Ratio	(95%CI), p-value
Either	Never	350/823	1	
	Any	61/270	0.53	(0.37-0.75) 0.003
	≤1	15/122	0.37	(0.20-0.67) 0.001
	(1, 4]	27/112	0.53	(0.32-0.87) 0.01
	>4	19/36	0.83	(0.44-1.55) 0.55
BRCA1	Never	290/719	1	
	Any	43/194	0.58	(0.39-0.85) 0.006
	≤1	9/94	0.33	(0.16-0.69) 0.003
	(1, 4]	18/72	0.62	(0.35-1.11) 0.11
	>4	16/28	0.93	(0.47-1.85) 0.84
BRCA2	Never	60/104	1	
	Any	18/76	0.39	(0.19-0.83) 0.01
	≤1	6/28	0.41	(0.14-1.25) 0.12
	(1, 4]	9/40	0.37	(0.13-1.00) 0.05
	>4	3/8	0.43	(0.08-2.36) 0.33

* Adjusted by chemotherapy (yes/no) and radiotherapy (yes/no)

Table 3
Association between Tamoxifen and contralateral breast cancer by Tamoxifen duration,
with four or more years elapsed from first cancer to contralateral cancer

Mutation	Tam used year	Number of Tamoxifen users Bilatera/Unilaterl		
			OR *	(95%CI), p-value
Either	Never	228/327	1	
	Any	37/126	0.43	(0.27-0.67) 0.0003
	<=1	6/25	0.25	(0.09-0.69) 0.007
	(1, 4]	12/65	0.30	(0.15-0.60) 0.008
	>4	19/36	0.75	(0.40-1.42) 0.38
BRCA1	Never	188/280	1	
	Any	27/86	0.48	(0.29-0.81) 0.006
	<=1	3/17	0.21	(0.06-0.75) 0.02
	(1, 4]	8/41	0.34	(0.15-0.79) 0.01
	>4	16/28	0.85	(0.42-1.70) 0.64
BRCA2	Never	40/47	1	
	Any	10/40	0.27	(0.10-0.72) 0.01
	<=1	3/8	0.33	(0.06-1.85) 0.21
	(1, 4]	4/24	0.22	(0.05-0.86) 0.03
	>4	3/8	0.33	(0.05-2.04) 0.23

* Adjusted by chemotherapy (yes/no) and radiotherapy (yes/no)

Table 4
Association between Tamoxifen and contralateral breast cancer by Tamoxifen duration, by menopausal status at time of second primary cancer in the bilateral case. BRCA1 and BRCA2 combined

Mutation	Tamoxifen use (years)	Number of Tamoxifen users Bilateral/Unilateral		
			Odds Ratio	(95% CI); p-value
Pre-menopausal (n = 189 cases)	Never	175/489	1	
	Any	19/96	0.59	(0.29-1.18) 0.14
	≤1	4/60	0.45	(0.15-1.39) 0.17
	(1, 4]	9/27	0.76	(0.29-2.15) 0.60
	>4	6/9	0.59	(0.11-3.17) 0.54
Post-menopausal (n = 203 cases)	Never	165/308	1	
	Any	38/164	0.58	(0.35-0.95) 0.03
	≤1	10/60	0.38	(0.16-0.86) 0.02
	(1, 4]	16/77	0.54	(0.26-1.12) 0.10
	>4	12/27	1.07	(0.45-2.51) 0.87

* Adjusted by chemotherapy (yes/no) and radiotherapy (yes/no)