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ORIGINAL REPORT

Relationship Between Potentially Modifiable Lifestyle Factors and Risk of Second Primary Contralateral Breast Cancer Among Women Diagnosed With Estrogen Receptor–Positive Invasive Breast Cancer

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ABSTRACT

Purpose
An outcome of considerable concern among breast cancer survivors is the development of second primary breast cancer. However, evidence regarding how potentially modifiable lifestyle factors modulate second breast cancer risk is limited. We evaluated the relationships between obesity, alcohol consumption, and smoking on risk of second primary invasive contralateral breast cancer among breast cancer survivors.

Methods
Utilizing a population-based nested case-control study design, we enrolled 365 patients diagnosed with an estrogen receptor–positive (ER+) first primary invasive breast cancer and a second primary contralateral invasive breast cancer, and 726 matched controls diagnosed with only an ER+ first primary invasive breast cancer. Obesity, alcohol use, and smoking data were ascertained from medical record reviews and participant interviews. Using conditional logistic regression we evaluated associations between these three exposures and second primary contralateral breast cancer risk.

Results
Obesity, consumption of ≥ 7 alcoholic beverages per week, and current smoking were all positively related to risk of contralateral breast cancer (odds ratio [OR], 1.4; 95% CI, 1.0 to 2.1; OR, 1.9; 95% CI, 1.1 to 3.2; and OR, 2.2; 95% CI, 1.2 to 4.0, respectively). Compared with women who consumed fewer than seven alcoholic beverages per week and were never or former smokers, women who consumed ≥ 7 drinks per week and were current smokers had a 7.2-fold (95% CI, 1.9 to 26.5) elevated risk of contralateral breast cancer.

Conclusion
Our population-based study adds to the limited available literature and suggests that obesity, smoking, and alcohol consumption influence contralateral breast cancer risk, affording breast cancer survivors three means of potentially reducing this risk.

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INTRODUCTION

High incidence rates of invasive breast cancer, coupled with the disease's now greater than 90% 5-year survival rate in the United States, have resulted in a large and ever growing number of breast cancer survivors. Second primary contralateral breast cancer is an outcome of particular concern to breast cancer survivors since they have a two to six times greater risk of developing a contralateral breast cancer than women in the general population have of developing a first breast cancer.[1] While adjuvant hormone therapy can reduce contralateral breast cancer risk by 47%,[2] little information on other factors within a woman's control that can influence this risk is known.

Obesity is a potential risk factor for contralateral breast cancer. While two early studies found no relationship between obesity and second primary breast cancer risk,[3,4] four more recent studies reported positive associations.[5-8] Data with respect to alcohol consumption and smoking are also mixed with most studies finding modest increases in risk that did not reach statistical signficance.[3,4,7-9] These studies have been limited by relatively small sample sizes, although a large recently published case-control study found that regular alcohol consumption was associated

with a 30% increase in risk of contralateral breast cancer, but that smoking was not.[9]

We evaluated the relationship between three potentially modifiable lifestyle factors, body mass index (BMI), alcohol use, and smoking, and risk of second primary contralateral breast cancer among survivors of invasive estrogen receptor (ER) –positive breast cancer. Given the growing number of breast cancer survivors, identification of potentially modifiable risk factors for second contralateral tumors could have broad clinical and personal relevance to this population.

METHODS

We conducted a population-based nested case-control study of the risk of second primary invasive contralateral breast cancer that was approved by the Fred Hutchinson Cancer Research Center's institutional review board. Patients and controls were identified from the underlying cohort of 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 from January 1, 1990, to September 30, 2005. Data from the population-based cancer registry that serves western Washington, the Cancer Surveillance System (a participant in the National Cancer Institute's Surveillance, Epidemiology and End Results program since 1974) was used to assemble this cohort.

Patient and Control Identification

Cancer Surveillance System was used to identify patients with second primary invasive contralateral breast cancer diagnosed in our cohort. Eligible participants were included regardless of vital status. All women who were alive provided informed consent, and deceased women were enrolled through an institutional review board–approved waiver of consent. Patients were defined as women who developed invasive cancer in the breast contralateral to their first breast cancer 6 months or longer after their first breast cancer diagnosis from July 1, 1990, to March 31, 2007, in our four county catchment area. A total of 446 eligible patients were identified of which 369 (83%) were enrolled. Controls were individually matched 2:1 to patients on age, year of diagnosis, county, race/ethnicity, and stage (localized *v* regional). In addition, controls had to be alive and reside in their county of diagnosis from their breast cancer diagnosis to at least the duration between their matched patient's first and second breast cancer diagnoses. A total of 982 eligible controls were identified of which 734 (75%) were enrolled.

Exposure Assessment

Data on demographic, epidemiologic, and clinical factors were ascertained from two sources—structured interviewer-administered telephone questionnaires and a detailed medical record review. Interviewers and record abstractors were blinded to our study's primary hypotheses, but not to case/control status. The telephone interview queried women on a variety of topics. Participant recall was enhanced through the use of showcards with common responses and individualized life-events calendars. Women were asked about breast cancer surgeries, radiation therapy, chemotherapy, and adjuvant hormone therapy. For hormone therapy data on specific medications used, patterns of use, and start and stop dates were collected. Women were also asked to recall their history of various established breast cancer risk factors. Self-reported data on height and weight at multiple time points including at the time of their first breast cancer diagnosis and at their assigned reference date (which for patients with contralateral breast cancer was the date of their contralateral breast cancer diagnosis and for controls was the date of their matched patient's contralateral breast cancer diagnosis) were collected. Lifetime alcohol consumption through reference date was collected through asking about the number of alcohol containing beverages women consumed at different times in their lives and when their patterns of use changed. Smoking history through reference date was assessed by determining whether women ever smoked, and then asking ever smokers about their smoking patterns, when they started smoking, and if they ever stopped.

Medical records were sought from multiple sources including oncology and primary care practices so that complete data on breast cancer treatments, clinical and pathologic tumor characteristics, and breast cancer risk factors could be abstracted. For the 103 patients with contralateral breast cancer and 161 controls who were deceased at enrollment, data were only collected from medical records.

For quality control purposes, the study coordinator evaluated a random 10% sample of all recorded telephone interviews to ensure study protocols were correctly followed. Similarly, a random 10% of medical records were rereviewed by our medical record coordinator to ensure that data were abstracted consistently.

Categorization of Exposures

BMI data from medical records were prioritized over self-reported data. Medical record data on BMI at first breast cancer diagnosis and reference data were available for 86% and 63% of all participants, respectively, and in total BMI data were available at first breast cancer diagnosis and reference date for 98% (355 patients with contralateral breast cancer and 712 controls) and 88% (309 patients with contralateral breast cancer and 649 controls) of participants, respectively. BMI categories were based on WHO criteria (reference category = BMI < 25.0 kg/m^2; overweight = BMI between 25.0 to 29.9 kg/m^2; obese = BMI ≥ 30 kg/m^2). With respect to BMI at reference date, there was 75% agreement ($\kappa = 0.63$) between self-reported and medical record-based BMI data that did not differ by case-control status (77% for patients and 74% for controls). In general, self-reported BMI was lower than BMI abstracted from medical records. Among those with data from both sources the mean self-reported BMI at reference date was 26.4 (standard deviation, 5.8), and the mean BMI from medical records was 28.2 (standard deviation, 6.2).

Data on alcohol use and smoking history relative to both first breast cancer diagnosis and reference date were ascertained only from self-report because of an inability to obtain reliable data on these exposures from medical records. Alcohol consumption was analyzed as average number of alcoholic beverages consumed per week at two time points: at the time of first breast cancer diagnosis and during the interval between first breast cancer diagnosis and reference date. Alcohol consumption was grouped into four categories (nondrinkers, $<$ 3 drinks/week, 3 to 6.9 drinks/week, and $\geq$ 7 drinks/week), and smoking was grouped into three categories (never, former, and current).

Statistical Analysis

Associations between BMI, smoking, and alcohol consumption and risk of second primary contralateral breast cancer were estimated by conditional logistic regression using Stata SE (Stata Corp, College Station, TX). As a result, all statistical models were implicitly adjusted for each of the matching variables. All analyses were also adjusted for adjuvant hormone therapy and chemotherapy, so the four patients with contralateral breast cancer and eight controls with missing data for one or both of these variables were excluded from all analyses, leaving 365 patients with contralateral breast cancer and 726 controls. Odds ratios (ORs) and 95% CIs were calculated as estimates of the relative risk. All statistical tests were two sided. We systematically assessed a series of potential confounders and effect modifiers (those listed in Table 1). Factors that changed our risk estimates by greater than 10% when adjusted for were considered to be confounders and included in our final statistical models. Based on this approach, ORs for BMI were additionally adjusted for use of menopausal hormone at first breast cancer diagnosis; ORs for alcohol use were additionally adjusted for BMI at reference date; and ORs for smoking were additionally adjusted for first-degree family history of breast cancer. Effect modification was assessed using likelihood ratio testing. None of the factors listed in Table 1, including adjuvant hormone therapy, had a statistically significant ($P < .05$) interaction with any of the main effects we assessed.

RESULTS

We compared patients and controls with respect to several factors (Table 1). Other than controls being more likely to have received adjuvant hormone therapy compared with patients ($P < .0001$), there were no other statistically significant differences between these two

Table 1. Characteristics of Patients With Contralateral Breast Cancer and Controls

Characteristic	Controls (n = 726)		Patients With Contralateral Breast Cancer (n = 365)		*P* for Difference Between Contralateral Patients and Controls
	No.	%	No.	%	
Demographic characteristics					
Age at first breast cancer diagnosis, years					
40-49	137	18.9	71	19.5	
50-59	197	27.1	96	26.3	
60-69	223	30.7	112	30.7	
70-79	169	23.3	86	23.6	.99
Reference age, years					
40-59	217	29.9	106	29.0	
60-69	231	31.8	116	31.8	
70-79	210	28.9	104	28.5	
80-88	68	9.4	39	10.7	.62
Year of first breast cancer diagnosis					
1990-1993	263	36.2	132	36.2	
1994-1997	245	33.7	121	33.2	
1998-2001	164	22.6	85	23.3	
2002-2005	54	7.4	27	7.4	.91
Race/ethnicity					
Non-Hispanic white	662	91.4	334	92.0	
Asian/Pacific Islander	28	3.9	12	3.3	
African American	18	2.5	9	2.5	
Native American	10	1.4	5	1.4	
Hispanic white	6	0.8	3	0.8	
Missing	2		2		.71
Treatments for first breast cancer					
Received radiation therapy for first breast cancer					
No	247	34.1	130	35.6	
Yes	478	65.9	235	64.4	
Missing	1		0		.61
Received chemotherapy for first breast cancer					
No	534	73.6	272	74.5	
Yes	192	26.4	93	25.5	.56
Duration of adjuvant hormone therapy for first breast cancer, years					
None	218	30.0	144	39.5	
< 1	99	13.5	50	13.7	
1-4	276	38.0	118	32.3	
≥ 5	134	18.5	53	14.5	> .0001
Tumor characteristics					
AJCC stage					
I	496	68.3	239	65.5	
II or III	230	31.7	126	34.5	.33
Lymph node involvement					
No	558	76.9	273	74.8	
Yes	168	23.1	92	25.2	.45
Tumor size, cm					
≤ 1.0	248	35.0	116	33.2	
1.1-2.0	314	44.3	141	40.4	
> 2.0	147	20.7	92	26.4	
Missing	17		16		.13
Established breast cancer risk factors					
First-degree family history of breast cancer					
No	511	74.5	235	70.4	
Yes	175	25.5	99	29.6	
Missing	40		31		.29

(continued on following page)

Table 1. Characteristics of Patients With Contralateral Breast Cancer and Controls (continued)

Characteristic	Controls (n = 726)		Patients With Contralateral Breast Cancer (n = 365)		*P* for Difference Between Contralateral Patients and Controls
	No.	%	No.	%	
Recency of menopausal hormone use at first breast cancer diagnosis					
Never user	342	49.9	172	51.2	
Former user	72	10.4	39	11.6	
Current estrogen alone user	144	20.9	70	20.8	
Current estrogen + progestin user	131	19.0	55	16.4	
Missing	37		29		.33
No. of full-term pregnancies					
Nulliparous	106	15.0	57	16.2	
1	93	13.2	45	12.8	
2	210	29.7	110	31.3	
3	166	23.5	70	19.9	
≥ 4	132	18.7	70	19.9	
Missing	19		13		.82

Abbreviation: AJCC, American Joint Committee on Cancer.

groups. Of our 365 contralateral patients, 303 were ER+, 54 were ER-negative, and 12 had an unknown ER status.

Compared with women with a BMI lower than 25.0 kg/m^2, those with a BMI ≥ 30.0 kg/m^2 had an elevated risk of contralateral breast cancer (Table 2). This was observed both for BMI at first breast cancer diagnosis and at reference date, though the latter risk estimate was within the limits of chance. The relationship between BMI and contralateral breast cancer was unchanged when the analysis was restricted only to BMI data abstracted from medical records (OR, 1.5; 95% CI, 1.0 to 2.2).

Alcohol consumption was also positively related to contralateral breast cancer risk when assessed at both first breast cancer diagnosis and over the interval between first breast cancer diagnosis and reference date (Table 2). Similarly, compared with never smokers, current smokers at both first breast cancer diagnosis and at reference date had elevated risks of contralateral breast cancer. The relationship with current smoking did not vary by pack years of smoking (data not shown). Though the number of women who were current smokers at the time of their first breast cancer diagnosis but had quit by their reference date was small (14 patients and 29 controls), among these women current smoking at first breast cancer diagnosis was not related to contralateral breast cancer risk (OR, 0.8; 95% CI, 0.2 to 3.3). These latter two observations suggest that recency of smoking is most relevant to risk.

Compared with women who consumed 0 to 6.9 drinks/week and were never smokers, those who consumed ≥ 7 drinks/week and were current smokers at either first breast cancer diagnosis or reference date had substantially higher risks of contralateral breast cancer (Table 3).

DISCUSSION

All three potentially modifiable risk factors we investigated were positively related to risk of second primary contralateral breast cancer. The 40% to 50% elevation in risk associated with obesity we observed is consistent with the 58% elevation in contralateral breast cancer risk women with a BMI ≥ 30 kg/m^2 had compared with women with a BMI lower than 25 kg/m^2 enrolled in the National Surgical Adjuvant Breast and Bowel Project B-14 randomized trial of adjuvant tamoxifen in patients with node-negative invasive ER+ breast cancer.[5] It is also consistent with the 56% elevation in risk of second primary breast cancer observed for women in the highest BMI quartile compared with women in the lowest quartile in a large population-based cohort of breast cancer survivors.[7] Thus, our study adds to the growing body of evidence from recent studies that obesity may be an important risk factor for second primary contralateral breast cancer. The mechanisms through which obesity confers an increased risk of contralateral breast cancer are likely to be quite similar to those which govern its well established relationship with risk of first primary breast cancer.[10] In postmenopausal women, adipose tissue is the primary producer of endogenous estrogens, and this is thought to be the primary pathway through which obesity confers an elevation in breast cancer risk. In addition, there is growing data to suggest that hyperinsulinemia may also be an important contributor to the relationship between obesity and breast cancer.[11]

We observed that consumers of ≥ 7 alcoholic beverages per week had a 90% increased risk of contralateral breast cancer. Our result is broadly consistent with the increased risk of contralateral breast cancer observed among women who had ever regularly consumed alcohol in a large recently published multicenter patient-control study.[9] Our risk estimate is higher though than the 20% increase in risk this prior study observed among women who on average consumed ≥ 1 drink per day. Other smaller studies have also observed modest positive associations that were not statistically significant.[3,7,8] While the reasons for this difference in the magnitude of the association are unclear, one potential explanation is that our study was restricted to women whose first breast cancer was ER+. Similar to obesity, the relationship between alcohol use and risk of first breast cancer is well established.[12] The primary mechanism through which it is thought to elevate risk is hormone since alcohol consumption directly increases endogenous estrogen levels in postmenopausal women.[13,14] There is also some evidence that alcohol use is more strongly related to risk of ER+ versus ER-negative breast cancer.[15,16] Thus,

Table 2. Relationship Between Body Mass Index, Alcohol Consumption, and Smoking and Risk of Contralateral Breast Cancer

Characteristic	Controls (n = 712)		Patients With Contralateral Breast Cancer (n = 355)		OR*	95% CI
	No.	%	No.	%		
Body mass index at first breast cancer diagnosis, kg/m^2						
< 25	317	44.5	133	37.5	1.0	Reference
25-29.9	213	29.9	114	32.1	1.3	0.9 to 1.8
≥ 30	182	25.6	108	30.4	1.5	1.0 to 2.1†
Body mass index at reference date, kg/m^2						
< 25	254	39.3	110	35.6	1.0	Reference
25-29.9	222	34.0	93	30.1	1.0	0.7 to 1.5
≥ 30	173	26.7	106	34.3	1.4	1.0 to 2.1
Average alcohol consumption at first breast cancer diagnosis, drinks/week						
None	280	49.4	121	46.0	1.0	Reference
< 3	144	25.4	70	26.6	1.6	1.0 to 2.5†
3-6.9	62	10.9	29	11.0	1.4	0.7 to 2.5
≥ 7	81	14.3	43	16.4	1.7	1.0 to 2.9†
Average alcohol consumption between first breast cancer diagnosis and reference date, drinks/week						
None	270	47.6	119	45.3	1.0	Reference
< 3	149	26.3	75	28.5	1.6	1.0 to 2.4
3-6.9	75	13.2	26	9.9	1.0	0.5 to 1.8
≥ 7	73	12.9	43	16.4	1.9	1.1 to 3.2†
Smoking status at first breast cancer diagnosis						
Never smoker	298	52.2	126	47.6	1.0	Reference
Former smoker	186	32.6	88	33.2	1.2	0.8 to 1.7
Current smoker	87	15.2	51	19.3	1.8	1.1 to 3.2†
Smoking status at reference date						
Never smoker	298	52.2	126	47.6	1.0	Reference
Former smoker	215	37.7	102	38.5	1.2	0.8 to 1.7
Current smoker	58	10.2	37	14.0	2.2	1.2 to 4.0†

Abbreviation: OR, odds ratio.

*ORs and 95% CIs were estimated using conditional logistic regression and are implicitly adjusted for each of the matching variables (age and year of first breast cancer diagnosis, county, race/ethnicity, stage, and survival time). In addition, all ORs are adjusted for adjuvant hormonal therapy and chemotherapy. ORs for body mass index are also adjusted for use of menopausal hormone therapy at first breast cancer diagnosis. ORs for alcohol use are also adjusted for body mass index at reference date. ORs for smoking are also adjusted for first degree family history of breast cancer.

†$P < .05$.

based on the available biologic and epidemiologic evidence, the relationship between alcohol use and contralateral breast cancer may be stronger among women whose first breast cancer was ER+.

Our observation that current smokers have a substantial 2.2-fold increased risk of contralateral breast cancer is somewhat consistent with the results of two previous reports, although the magnitude of the association we observed is again higher. One of these studies observed a 70% increased risk among women who smoked more than a pack a day,[4] and the other reported a 24% increased risk among ever smokers[3] (compared with never smokers), but neither result was statistically significant. In contrast, the previously mentioned large multicenter case-control study that found a positive association with alcohol, did not observe a relationship between ever having smoked during the interval between first breast cancer diagnosis and reference date and contralateral breast cancer risk.[9] However, it did not separate former and current smokers, making it somewhat difficult to directly compare our results. Lastly, a study evaluating risk of second primary breast cancer regardless of laterality found that current smoking was not related to risk.[7]

Unlike obesity and alcohol use, smoking is not a well established risk factor for postmenopausal breast cancer despite biologic plausibility for a positive association. Tobacco smoke contains carcinogens that are genotoxic to the rodent mammary gland,[17] and in humans tobacco carcinogen DNA adducts have been found in breast tissue[18,19] and these carcinogens can be metabolically activated in breast epithelial cells.[20,21] Inconsistency in published results from epidemiologic studies may due to evolving smoking patterns in women. Several recent studies indicate that smoking initiation at a young age and/or before a first full-term pregnancy may be more strongly related to breast cancer risk than is initiation at older ages.[22-25] In addition, greater intensity and duration of smoking appears to be positively associated with risk in several recent cohort and patient-control studies.[24-28] Thus, earlier studies of smoking and breast cancer may have failed to find an association with risk because too few women included started smoking at a young age or had smoked at sufficient intensities or durations to detect an association. The interaction between alcohol consumption and smoking in relation to contralateral breast cancer observed here has not been previously reported. While our study had limited statistical power to assess interactions, our results suggest that smoking may confer an increased risk of contralateral breast cancer independent of alcohol use, alcohol's effect may depend on concurrent smoking, and women with higher levels of

Table 3. Joint Effects of Alcohol Consumption and Smoking on Risk of Contralateral Breast Cancer

Parameter	Controls (n = 567)		Patients With Contralateral Breast Cancer (n = 263)		Odds Ratio*	95% CI
	No.	%	No.	%		
Alcohol consumption and smoking at first breast cancer diagnosis						
0-6.9 drinks/week and never/former smoker	416	73.4	185	70.3	1.0	Reference
0-6.9 drinks/week and current smoker	70	12.4	35	13.3	1.4	0.8 to 2.4
≥ 7 drinks/week and never/former smoker	65	11.5	27	10.3	0.9	0.5 to 1.8
≥ 7 drinks/week and current smoker	16	2.8	16	6.1	3.7	1.4 to 9.8†
P for interaction				.078		
Alcohol consumption and smoking at reference date						
0-6.9 drinks/week and never/former smoker	445	78.5	197	74.9	1.0	Reference
0-6.9 drinks/week and current smoker	49	8.6	23	8.8	1.5	0.8 to 2.8
≥ 7 drinks/week and never/former smoker	64	11.3	29	11.0	1.2	0.6 to 2.1
≥ 7 drinks/week and current smoker	9	1.6	14	5.3	7.2	1.9 to 26.5†
P for interaction				.047		

*Odds ratios and 95% CIs were estimated using conditional logistic regression and are implicitly adjusted for each of the matching variables (age and year of first breast cancer diagnosis, county, race/ethnicity, stage, and survival time). Risk estimates are additionally adjusted for use of adjuvant hormone therapy, chemotherapy, body mass index at reference date, and first degree family history of breast cancer.
†$P < .05$.

alcohol consumption who are current smokers may have particularly high risks of contralateral breast cancer. However, these relationships require confirmation.

A potential limitation of all patient-control studies is recall bias. Our BMI results were not impacted by this bias because our primary source of anthropometric data was medical records and risks were unchanged when analyses were restricted to data only from medical records. In contrast, data on smoking and alcohol use could not be reliably obtained from medical records and so analyses are based only on self-reported data. Consequently, data from enrolled deceased women could not be included. The extent of the potential resulting biases is unknown. Encouragingly, when we restricted our BMI analyses to self-reported data from alive women, the same association was observed when women with a BMI ≥ 30 kg/m^2 at first breast cancer diagnosis were compared with women with a BMI lower than 25 kg/m^2 (OR based on medical record data including both alive and deceased women: 1.6; 95% CI, 1.1 to 2.2 *v* OR based on self-reported data from alive women only: 1.6; 95% CI, 1.0 to 2.5). Given the considerable correlation within our three exposures between the two time points of interest, date of first breast cancer diagnosis and reference date (particularly for BMI and alcohol use), it was difficult to evaluate how changes in these exposures over time influenced contralateral breast cancer risk. However, in a subanalysis of women who were current smokers at the time of their first breast cancer diagnosis, but had quit smoking by reference date, the fact that they were current smokers at their first breast cancer diagnosis did not impact their risk of contralateral breast cancer. This suggests that recency of smoking may be most relevant to contralateral breast cancer risk. With respect to the generalizability of our results, this study was limited to women with ER+ first primary breast cancers, so the extent to which the risk factors studied influence risk of contralateral breast cancer among women with ER-negative first breast cancers could not be assessed. Also, this study included women diagnosed with their first breast cancer as long ago as 1990 when patterns or hormone therapy use were different then they are now. As a result fewer women ever used hormone therapy, or used if for a duration conferring maximal clinical benefit, than women today. While our analyses were adjusted for use of hormone therapy, interactions with hormone therapy could not be assessed given the size of our study.

Few studies, most with relatively small sample sizes, have evaluated the influence that potentially modifiable lifestyle factors have on risk of second primary contralateral breast cancer. Identifying such factors could be both of broad public health relevance and of individual importance to the growing number of breast cancer survivors. Our population-based study adds to the limited available literature and suggests that obesity, smoking, and alcohol are all positively related to risk affording breast cancer survivors three means of potentially reducing their risk of contralateral breast cancer.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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