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Original Contribution

Alcohol Intake and Cigarette Smoking and Risk of a Contralateral Breast Cancer

The Women's Environmental Cancer and Radiation Epidemiology Study

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Women with primary breast cancer are at increased risk of developing second primary breast cancer. Few studies have evaluated risk factors for the development of asynchronous contralateral breast cancer in women with breast cancer. In the Women's Environmental Cancer and Radiation Epidemiology Study (1985–2001), the roles of alcohol and smoking were examined in 708 women with asynchronous contralateral breast cancer (cases) compared with 1,399 women with unilateral breast cancer (controls). Cases and controls aged less than 55 years at first breast cancer diagnosis were identified from 5 population-based cancer registries in the United States and Denmark. Controls were matched to cases on birth year, diagnosis year, registry region, and race and countermatched on radiation treatment. Risk factor information was collected by telephone interview. Rate ratios and 95% confidence intervals were estimated by using conditional logistic regression. Ever regular drinking was associated with an increased risk of asynchronous contralateral breast cancer (rate ratio = 1.3, 95% confidence interval: 1.0, 1.6), and the risk increased with increasing duration ($P = 0.03$). Smoking was not related to asynchronous contralateral breast cancer. In this, the largest study of asynchronous contralateral breast cancer to date, alcohol is a risk factor for the disease, as it is for a first primary breast cancer.

alcohol drinking; breast neoplasms; neoplasms, second primary; smoking

Abbreviations: CI, confidence interval; RR, rate ratio; WECARE, Women's Environmental Cancer and Radiation Epidemiology.

The risk of developing asynchronous contralateral breast cancer, a primary breast cancer occurring in the opposite breast subsequent to a first breast cancer diagnosis in 1 breast, in female survivors of breast cancer is considerably higher than the risk of developing a first primary breast cancer in unaffected women (1). The population of women with breast cancer have a higher prevalence of all breast cancer risk factors, both genetic and nongenetic, than women without breast cancer. It would be expected that women who go on to develop asynchronous contralateral breast cancer would have an even higher prevalence of risk factors than those who develop only 1 primary, although there may be mitigating factors such as the treatment received for the first primary and changes in behavior. Few studies have examined the role of alcohol intake or cigarette smoking, 2 potentially modifiable risk factors, in the development of asynchronous contralateral breast cancer. Given the high level of risk in these women, clarifying the role of modifiable risk factors in asynchronous contralateral breast cancer in women with breast cancer is important.

A number of meta-analyses confirm that alcohol is a risk factor for both pre- and postmenopausal first primary breast cancer, although the magnitude of increased risk associated with consuming 1 or more drinks per day is moderate (2–4). Recent studies confirm this finding (5, 6). Thus far, a significant association between alcohol intake and second primary breast cancer has not been observed (7–9), although 2 of the studies observed elevated risk estimates of 1.09 and

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1.11 associated with recent or ever drinking prior to the first diagnosis, respectively (7, 9). A variety of mechanisms, which may all contribute to the relation, have been proposed to explain the association between alcohol and breast cancer including estrogen metabolism, acetaldehyde mutagenesis, oxidation and free radicals, and 1-carbon metabolism (10).

Cigarette smoking has been more controversial as a possible risk factor for breast cancer with inconsistent results in the literature (11, 12). Conflicting results may be due to the competing effects of smoking at different ages. In some studies, increased risk has been associated specifically with smoking at an early age during breast development, although observations regarding the effect of early smoking vary (13–15). The relation between smoking and second primary breast cancer has also been inconsistent, with some studies observing evidence of an association (16, 17) and others not (7–9).

In this study, we evaluate the evidence for an association between alcohol intake and cigarette smoking and the development of asynchronous contralateral breast cancer among women with a first diagnosis of breast cancer from the Women's Environmental Cancer and Radiation Epidemiology (WECARE) Study.

MATERIALS AND METHODS

The WECARE Study is a multicenter, population-based, nested case-control study where women with asynchronous contralateral breast cancer serve as cases and women with unilateral breast cancer serve as matched controls (18). Additional detail on data collection has been reported previously (19). All participants were identified through 5 population-based tumor registries, 4 in the United States (Los Angeles County Cancer Surveillance Program, Cancer Surveillance System of the Fred Hutchinson Cancer Research Center, State Health Registry of Iowa, Cancer Surveillance Program of Orange County/San Diego-Imperial Organization for Cancer Control) and 1 in Denmark (the Danish Breast Cancer Cooperative Group Registry supplemented by data from the Danish Cancer Registry).

Study population

Women were eligible as cases if they were diagnosed between January 1, 1985, and December 31, 2000, and were aged less than 55 years with a first primary invasive breast cancer that did not spread beyond the regional lymph nodes at diagnosis and a second primary in situ or invasive breast cancer diagnosed in the contralateral breast at least 1 year after the first breast cancer diagnosis. The asynchronous contralateral breast cancer had to have been diagnosed no later than December 31, 2001. Case patients were required to have resided in the same reporting area at the time of diagnosis of both cancers, to have had no prior or intervening cancer diagnosis between their first and second primary breast cancers, and to be alive at the time of contact. Two control subjects were individually matched to each case on year of birth, year of diagnosis, registry region, and race and were 1:2 counter-matched on registry-reported radiation exposure, so that each triplet consisted of 1 radiation-unexposed and 2 radiation-exposed subjects. In addition, controls had to meet the following criteria: 1) diagnosed since January 1, 1985, with a first primary invasive breast cancer while residing in 1 of the study reporting areas; 2) residing on the reference date (the date of first diagnosis plus "at-risk interval," the time between the first and second diagnoses, of the matched case) in the same registry reporting area where they were diagnosed with their breast cancer; 3) never diagnosed (by reference date) with a second primary breast cancer or any other cancer; 4) alive at the time of contact; and 5) without prophylactic mastectomy of the contralateral breast following diagnosis of their first primary. The control sampling is accounted for in the analysis by the inclusion of sampling weights. The design has been discussed in detail previously (18).

A total of 998 women with asynchronous contralateral breast cancer were eligible and approached for inclusion in the study as cases, and 2,112 women with unilateral breast cancer were eligible as controls. Of these potential participants, 708 cases (71%) and 1,399 controls (66%) completed the interview and had a blood sample drawn.

Data collection

All participants in the WECARE Study were interviewed over the telephone to obtain information on known and suspected risk factors for breast cancer including the following: personal demographics; age at menarche, first birth, and menopause; parity and lactation; body size; and family history of cancer. All questions were asked in reference to the period before the reference date (defined above). The following descriptions reflect the actual wording used in the questionnaire or by the interviewer. The specific information collected on alcohol and smoking consisted of whether the women had ever smoked cigarettes or drunk any alcoholic beverages regularly (at least 1 cigarette a day for 6 months or longer or at least 1 drink per month, respectively) before the reference date, how old they were when they first started smoking cigarettes or drinking alcoholic beverages regularly, whether they had stopped smoking or drinking regularly, at what age they last stopped, how many total years they smoked or drank regularly, and, during periods when they smoked regularly, on average, how many cigarettes they usually smoked per day, week, or month. With respect to alcohol consumption, they were told that 1 drink is equal to 1 bottle or can of beer, 1 glass of wine or bottle of wine cooler, or 1 cocktail, shot, or mixed drink of liquor and then asked to describe their average alcohol consumption before the reference date in categories (never or less than 1 drink each month, 1–3 drinks each month, 1 drink each week, 2–4 drinks each week, 5 or 6 drinks each week, 1 drink each day, 2 or 3 drinks each day, or 4 or more drinks each day). Medical records, pathology reports, and hospital charts were used to collect detailed information on treatment and tumor characteristics. The study protocol was approved by the institutional review boards at each study site and by the ethical committee system in Denmark.

Statistical analysis

We used conditional logistic regression analysis with the inclusion of a log weight covariate in the model where the

Table 1. Characteristics of Women With Unilateral and Asynchronous Contralateral Breast Cancer, the Women's Environmental Cancer and Radiation Epidemiology Study, 1985–2001

	Breast Cancer			
	Unilateral (n = 1,399)		Asynchronous Contralateral (n = 708)	
	No.	%[a]	No.	%
Matched characteristics				
Registry				
Iowa	222	15.9	113	16.0
Orange County/San Diego, California	231	16.5	118	16.7
Los Angeles County, California	390	27.9	199	28.1
Seattle, Washington	198	14.2	99	14.0
Denmark	358	25.6	179	25.3
Race				
Non-Hispanic white	1,288	92.1	649	91.7
Hispanic white	48	3.4	24	3.4
Black	39	2.8	21	3.0
Other	24	1.7	14	2.0
Mean age at first diagnosis, years (range)	45 (23–55)		46 (24–55)	
Mean age at reference date, years[b] (range)	51 (27–69)		51 (27–71)	
Mean at-risk period, years (range)	5 (1–16)		5 (1–16)	
Countermatched characteristic				
Radiation treatment				
No	266	50.2	362	51.1
Yes	1,133	49.8	346	48.9
Other characteristics				
Year of second diagnosis				
1986–1988			21	3.0
1989–1991			75	10.6
1992–1994			137	19.4
1995–1997			202	28.5
1998–2001			273	38.6
Family history[c] of breast cancer				
No	1,088	77.9	472	66.7
Yes	285	20.4	225	31.8
Unknown	26	1.8	11	1.6
Histology of first breast cancer				
Lobular	131	8.7	90	12.7
Medullar	51	3.4	33	4.7
Ductal and other	1,213	87.9	584	82.6
Stage of first breast cancer				
Localized	916	64.3	506	71.5
Regional	483	35.7	202	28.5
Chemotherapy				
No	629	42.5	386	54.5
Yes	770	57.5	322	45.5
Hormone therapy				
No	909	66.3	511	72.2
Yes	488	33.7	197	27.8

[a] Proportions are weighted for the countermatching with the exception of factors contributing to the study matching schema.

[b] "Reference date" is the date of diagnosis for asynchronous contralateral breast cancer and the corresponding date for unilateral breast cancer.

[c] First-degree family history.

coefficient of this log weight is fixed at 1 (i.e., an offset in the model). The weights used the numbers of registry-reported, radiation-exposed and -unexposed women in the risk set to account for the countermatched sampling design (18, 20). Further, because controls were independently sampled from the failure time risk sets, the estimated parameters are rate ratios in the proportional hazards model for cohort data (21), and standard likelihood methods apply (22). Smoking and alcohol consumption were each examined as ever regular use (yes/no), regular use during the at-risk period (yes/no), lifetime duration in tertiles defined in controls versus never use, and age at starting drinking or smoking. Consumption during the at-risk period was defined as starting prior to or during the period between first diagnosis and the reference date and stopping during or after the period between the first diagnosis and the reference date. The average smoking amount was defined as half a pack per day or less and greater than half a pack per day versus never smoked and also as pack-years in tertiles versus never smoked. Average alcohol consumption, which was collected as categories described above, was defined as less than 1 drink per day and 1 drink per day or more compared with never drinking. After adjusting for age in models examining ever versus never drinking and smoking, we tested the following potential confounders: education, first-degree family history of breast cancer, body mass index (both at first diagnosis and at the reference date), age at menarche, age at menopause, stage of first primary, histology of first primary, exposure to chemotherapy, exposure to radiation treatment, use of tamoxifen, number of full-term pregnancies, age at first full-term pregnancy, and ever breastfeeding. In addition, to test for mutual confounding, ever regular smoking was added to models of alcohol drinking, and ever regular drinking was added to models of smoking. As there was no indication of confounding, defined as a change in the rate ratio estimate of 10% or more over the rate ratio from the

Table 2. The Age-adjusted Association Between Alcohol Drinking and the Risk of Developing Asynchronous Contralateral Breast Cancer, the Women's Environmental Cancer and Radiation Epidemiology Study, 1985–2001

	Breast Cancer				Rate Ratio[a]	95% Confidence Interval
	Unilateral		Asynchronous Contralateral			
	No.	%[b]	No.	%		
Ever drank regularly						
No	550	42.4	275	39.0	1.0	
Yes	846	57.6	431	61.0	1.3	1.0, 1.6
Ever drank regularly during at-risk period[c]						
No	672	52.0	348	49.3	1.0	
Yes	722	48.0	358	50.7	1.2	0.9, 1.5
Lifetime duration of drinking						
Never	550	42.4	275	39.2	1.0	
<20 years	279	19.4	137	19.5	1.2	0.9, 1.7
20–<30 years	286	19.3	143	20.4	1.3	0.9, 1.7
≥30 years	276	18.9	147	20.9	1.4	1.0, 1.9
P_{trend}[d]						0.03
Average drinking amount						
Never	550	43.1	275	39.5	1.0	
<1 drink/day	659	45.2	338	48.5	1.3	1.0, 1.7
≥1 drink/day	171	11.7	84	12.1	1.2	0.8, 1.7
P_{trend}[d]						0.16
Starting age						
Never	550	42.4	275	39.0	1.0	
≥20 years of age	526	34.5	282	40.0	1.4	1.1, 1.8
<20 years of age	315	23.1	148	21.0	1.1	0.8, 1.5

[a] Accounting for countermatching and adjusted for age at first diagnosis.
[b] Proportions are weighted for the countermatching.
[c] Consumption during the at-risk period was defined as starting prior to or during the period between the first diagnosis and the reference date and stopping during or after the period between the first diagnosis and the reference date.
[d] Test for trend across categories.

age-adjusted model, only the age-adjusted models are presented. We performed tests for trend across categories of duration and consumption. All analyses were conducted using SAS, version 9.1, software (SAS Institute, Inc., Cary, North Carolina), and a 2-sided $P < 0.05$ was considered significant.

RESULTS

Table 1 shows selected characteristics of the WECARE Study population. The 2 groups were similar on all matched characteristics. Women with asynchronous contralateral breast cancer were more likely to have a family history of breast cancer. The majority (67%) of second diagnoses occurred in 1995 or later. In addition, 56% of cases and 49% of controls were interviewed within 5 years of the reference date, and 88% of cases and 86% of controls were interviewed within 10 years. Table 2 shows that ever regular drinking was associated with an elevated risk of developing asynchronous contralateral breast cancer (rate ratio (RR) = 1.3, 95% confidence interval (CI): 1.0, 1.6), although the increased risk associated with drinking specifically after the first diagnosis (the at-risk period) did not achieve statistical significance (RR = 1.2, 95% CI: 0.9, 1.5). The risk increased with increasing lifetime duration of drinking ($P_{trend} = 0.03$). We observed no apparent trend associated with the average amount of alcohol consumed. The risk of asynchronous contralateral breast cancer increased with later initiation of drinking (at age 20 or more years) but not with early initiation (before age 20 years). We did not observe any differences in the risks associated with the duration of drinking prior to the first pregnancy, adjusted for the age at first full-term pregnancy: began drinking after first pregnancy (RR = 1.5, 95% CI: 1.1, 2.1); drank <7 years before first pregnancy (RR = 1.4, 95% CI: 1.0, 1.9); drank ≥7 years before first pregnancy (RR = 1.2, 95% CI: 0.8, 1.7), versus parous and never drank. There was no evidence for any association with smoking (Table 3) nor any consistent pattern with smoking before the first pregnancy, adjusted for age at first full-term pregnancy: began smoking after first pregnancy (RR = 1.6, 95% CI: 1.0, 2.5); smoked

Table 3. The Age-adjusted Association Between Cigarette Smoking and the Risk of Developing Asynchronous Contralateral Breast Cancer, the Women's Environmental Cancer and Radiation Epidemiology Study, 1985–2001

	Breast Cancer				Rate Ratio[a]	95% Confidence Interval
	Unilateral		Asynchronous Contralateral			
	No.	%[b]	No.	%		
Ever regularly smoked						
No	701	49.9	349	49.3	1.0	
Yes	698	50.1	359	50.7	1.1	0.9, 1.6
Ever smoked regularly during at-risk period[c]						
No	1,108	79.6	542	76.9	1.0	
Yes	290	20.4	163	23.1	1.2	0.9, 1.5
Lifetime duration of smoking						
Never	701	49.9	349	49.4	1.0	
<20 years	323	23.4	150	21.2	1.0	0.8, 1.3
≥20 years	374	26.7	207	29.3	1.1	0.9, 1.5
P_{trend}[d]						0.36
Average smoking amount						
Never	701	49.9	349	49.7	1.0	
≤½ pack/day	358	25.6	180	25.6	1.0	0.8, 1.3
>½ pack/day	337	24.5	173	24.6	1.1	0.8, 1.4
P_{trend}[d]						0.57
Pack-years of smoking						
Never	701	50.0	349	49.9	1.0	
<6	235	17.2	94	13.4	0.8	0.6, 1.1
6–<19	232	16.4	132	18.9	1.3	1.0, 1.8
≥19	227	16.4	125	17.9	1.1	0.8, 1.4
P_{trend}[d]						0.27
Starting age						
Never	701	49.9	349	49.3	1.0	
≥20 years of age	225	16.0	104	14.7	1.0	0.8, 1.4
<20 years of age	473	34.1	255	36.0	1.1	0.9, 1.4

[a] Accounting for countermatching and adjusted for age at first diagnosis.
[b] Proportions are weighted for the countermatching.
[c] Smoking during the at-risk period was defined as starting prior to or during the period between the first diagnosis and the reference date and stopping during or after the period between the first diagnosis and the reference date.
[d] Test for trend across categories.

<6 years before first pregnancy (RR = 1.0, 95% CI: 0.7, 1.4); smoked ≥6 years before first pregnancy (RR = 1.3, 95% CI: 1.0, 1.8), versus parous and never smoked. We did not observe any difference in the effect of smoking or alcohol by categories of radiation exposure or any difference in the effect of alcohol by tamoxifen use (data not shown). We also did not observe consistent differences in results across categories when we conducted the analysis by the time between reference date and interview in 3 categories, 0–5 years, 6–10 years, and >10 years (data not shown).

DISCUSSION

In the WECARE Study, we found that consuming alcohol, particularly over longer periods of time, was associated with an increased risk of asynchronous contralateral breast cancer. We did not find evidence that smoking cigarettes increased the risk of this disease. Our results differ from previous studies that did not observe an increased risk of asynchronous contralateral breast cancer associated with alcohol (7–9). However, as with a first primary breast cancer, the effect of alcohol is modest and could be missed if the sample size was insufficient. Previous studies included 488, 77, or 136 cases (7–9) compared with the 708 cases in our study. Varying definitions and prevalences of drinking may also have contributed to the inconsistency among studies. In the largest previous study, only information on recent drinking prior to the first diagnosis was available, and the authors were unable to evaluate lifetime duration of drinking (7). We did not find a relation with reported average amount

consumed, but the women were asked to average their lifetime consumption, and changes in intake were not captured, including changes occurring around the time of the first diagnosis. Relatively few women in this population (12%) reported consuming 1 drink per day or more on average.

Previous studies of smoking and asynchronous contralateral breast cancer have yielded inconsistent results (7–9, 16, 17), similar to studies of first primary breast cancer (11, 12). As with alcohol, this inconsistency may be due to issues of study design, such as variation in sample size, smoking definitions, and smoking prevalences. Our results from the WECARE Study do not support the hypothesis that smoking is a risk factor for asynchronous contralateral breast cancer, although a small increased risk associated with smoking cannot be ruled out. Previous studies have not evaluated changes in drinking and smoking behavior. In the WECARE Study, we found that only a small proportion of women changed their drinking status after their first breast cancer diagnosis (10% of cases and 9% of controls), but the proportion who stopped smoking was greater (28% of cases and 29% of controls).

The WECARE Study included women who were aged less than 55 years at first diagnosis (mean age, 45 years among controls and 46 years among cases), although they were somewhat older at the reference date (mean age in both groups, 51 years). These women were younger than those in some other studies (7) but not others (8). However, there is no evidence that the effect of smoking or alcohol on the risk of first primary breast cancer differs by menopausal status (2–4, 10).

An important strength of the WECARE Study is that it is the largest case-control study conducted of asynchronous contralateral breast cancer to date that includes direct patient interview. We have also been able to detect other associations in their expected directions for fewer full-term pregnancies and early menarche (19), radiation treatment (23), and treatment of the first primary breast cancer with chemotherapy or tamoxifen (24). However, although we did capture some information on lifetime duration of smoking and alcohol consumption, the level of detail of the information collected was limited. We did not capture the changes in the patterns of consumption at various times of life. Although recall bias is a problem in case-control studies in general, whether or not it is an issue in our study is unclear, as both the cases and controls have been affected by breast cancer. In this study, cases and controls were matched on time since the first diagnosis, and the majority (56%) of cases were interviewed within 5 years and most (88%) within 10 years of the second diagnosis. It is likely that women can recall accurately whether they drank or smoked, and the broad categories used in the analysis of duration of drinking and smoking minimize the potential for misclassification errors in recall of when drinking and smoking began and ended. As with amount, we were unable to examine duration in greater detail. We were also unable to consider results by estrogen and progesterone status, as a considerable proportion of the cases were missing information on receptor status. Results from studies relating alcohol to first breast cancer according to hormone receptor status are inconsistent (10, 25). Further, if drinking and/or smoking adversely affects survival, and if fewer women who drink and/or smoke survive to be diagnosed with a second primary or to be included in the study after the second diagnosis, this could affect the relative risks reported here.

Women with a first primary unilateral breast cancer have an elevated risk of developing cancer in the contralateral breast. Although we did not observe an increased risk of asynchronous contralateral breast cancer associated with cigarette smoking, there are many other reasons to quit smoking including reducing the risk of smoking-related cancer or heart disease. Alcohol appears to be associated with an increased risk of asynchronous contralateral breast cancer.

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