Patterns of Alcohol Consumption and Breast Cancer Risk in the California Teachers Study Cohort

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Abstract

Alcohol consumption of approximately two drinks or more per day has been associated with elevated breast cancer risk in the California Teachers Study cohort as well as in many other populations. The objective of this analysis is to examine effects of age at drinking and drinking patterns and to identify effect modifiers. Of the 103,460 at-risk cohort members, age <85, who resided in California and completed the baseline alcohol assessment, 1,742 were diagnosed with invasive breast cancer after joining the cohort and before January 2001. Incident breast cancers were identified through the California Cancer Registry and follow-up for death and confirmation of continued California residence used various sources. Multivariate Cox proportional hazards regression models were used to estimate relative risks (RRs). Elevated breast cancer risk was most evident for recent drinking [RR = 1.28, 95% confidence interval (CI): 1.06–1.54 for ≥20 g/day *versus* nondrinkers], with no clear pattern for consumption during earlier periods of life. This elevation in risk was 32% among postmenopausal women (95% CI: 1.06–1.63) and 21% among pre/perimenopausal women (95% CI: 0.76–1.92). Highest risks associated with heavy alcohol consumption were observed among postmenopausal women with a history of biopsy-diagnosed benign breast disease (RR = 1.97, 95% CI: 1.39–2.79 compared to nondrinkers without benign breast disease) or who had used combination hormone replacement therapy (HRT) (RR = 2.24, 95% CI: 1.59–3.14 compared to nondrinkers who never used HRT). Recent alcohol consumption equivalent to two or more drinks per day increases the risk of invasive breast cancer, with the greatest RRs observed among heavy drinkers who are also postmenopausal and have a history of benign breast disease or who use HRT. (Cancer Epidemiol Biomarkers Prev 2004;13(3):405–411)

Introduction

The overall effects of alcohol consumption on breast cancer risk have been fairly well established. Most studies, including both case-control and cohort studies, have found that consuming two or more drinks per day is associated with an approximately 30% increase in risk (1–6). Recent alcohol consumption has also been associated with increased mammographic density but not benign breast disease, both important breast cancer risk factors (1); benign breast disease, however, has been associated with drinking at an early age (7). While most studies show little difference in risk based on beverage type, some do suggest that wine and liquor but not beer are associated with risk (8). Other aspects of drinking, including age at consumption and drinking patterns, as well as potentially modifying host factors, have been only minimally investigated (1, 2, 8, 9).

Several mechanisms have been proposed for how alcohol affects breast cancer risk (1). These mechanisms may include both early and late stage influences and may involve DNA damage, enhanced gland susceptibility, and elevated levels of steroid hormones (1, 10).

The objective of this analysis was to evaluate the effects of patterns of alcohol use (including age at drinking and ''sporadic'' *versus* ''daily'' drinking) on invasive breast cancer risk in the California Teachers Study (CTS) cohort, that is, a group of women among whom alcohol consumption of 20 or more grams per day is associated with elevated breast cancer risk (4). We also examined effect modification by a variety of health and lifestyle factors.

Materials and Methods

Study Population. The CTS cohort was established in 1995–1996 when 133,479 active and retired female teachers and administrators participating in the California State Teachers Retirement System returned a 16-page, mailed, optically scannable questionnaire (11). The questionnaire covered a wide variety of issues related to breast cancer risk and women's health, including recent and past alcohol consumption. For purposes of this analysis, we excluded women (in a hierarchical

Received 8/21/03; revised 10/31/03; accepted 11/12/03.

Grant support: Grant R01 CA77398 from the National Cancer Institute and by the California Breast Cancer Act of 1993, California Department of Health Services.

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manner) who were not residing in California at baseline (n = 8,866); who reported having been diagnosed with breast cancer before completing the baseline questionnaire, who were identified by the California Cancer Registry as having had a previous breast cancer, or did not adequately complete items related to a history of breast cancer (n = 6,267); who were age 85 or older at baseline (n = 1,994); or whose self-reported alcohol consumption data were missing (n = 1,745) or judged to be unreliable in part (n = 2,481 for past year consumption and n = 7,220 for consumption during earlier periods of life) or in total (n = 1,446). Of the 103,460 women included in this analysis, 1,742 were diagnosed with invasive breast cancer a month or more after joining the cohort and before January 1, 2001. Women diagnosed with *in situ* breast cancer (n = 369) and women who had moved out of California or died before January 1, 2001 (n = 5,089) contributed person-months to the analysis only up to the date of these events.

The CTS has been approved by the Institutional Review Boards of the State of California, the Northern California Cancer Center, the Public Health Institute, the University of California, Irvine, and the University of Southern California.

Alcohol Assessment. The number of drinks per week of beer, wine/champagne, and cocktails/liquor was assessed for three time periods: age 18–22 years, age 30–35 years, and the previous year. Response categories for usual frequency of consumption were none, ≤3/week, 4–10/week, 11–17/week, 18–24/week, and 25 or more per week. A drink was defined as: one bottle, can, or glass of beer; one glass of wine, champagne, or a wine cooler; or one cocktail, shot, or mixed drink of liquor. Grams of alcohol per drink were assigned as 13.2 for beer, 11.1 for wine, and 15.0 for liquor. Daily intake of grams of alcohol was calculated for each woman during each time period. For each beverage during each time period, we also assessed the number of days per week in which the respondent usually had at least one drink. We classified women as ''sporadic'' drinkers if they consumed alcohol on 4 or less days per week and ''daily'' drinkers if they consumed alcohol on 5 or more days per week. Average daily alcohol consumption for drinking pattern analyses continued to be based on a weekly calculation but expressed as grams per day, that is, grams of alcohol consumed per week was divided by seven (regardless of the number of days per week a woman reported drinking on).

Follow-Up. The CTS cohort is followed annually for cancer diagnosis, death, and change of address. Annual linkage between the California Cancer Registry (CCR) and the cohort membership is used to identify incident cancer cases. The CCR is a population-based cancer registry that is anchored in legislation that mandates reporting. It covers the entire state of California, has interstate agreements with 13 other states for case-sharing purposes, is estimated to be over 97% complete, and is part of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program. Thus, the CCR maintains the highest quality standards so that *all* cohort members residing in California effectively remain in active follow-up for cancer outcomes. Linkage between the CTS cohort and the CCR database is based on full name, date of birth, address, and social security number, and includes manual review of possible matches. Mortality files as well as reports from relatives are used to ascertain date and cause of death. Changes of address are obtained by annual mailings, responses from participants, and record linkages with multiple sources, including the California Department of Motor Vehicles and the US Postal Service National Change of Address database.

Data Analysis. Follow-up time was calculated as the number of months between joining the cohort (*i.e.*, the date the baseline questionnaire was completed) and either the date of invasive breast cancer diagnosis, the diagnosis of *in situ* breast cancer, the date of death, the date (or estimated date) the woman moved out of California, or December 31, 2000, whichever came first. *In situ* breast cancer cases were censored (rather than included in the analysis with invasive cases) for comparability with previous studies, because the type of treatment for *in situ* breast cancer may affect the risk of subsequent invasive breast cancer to varying degrees, and because there may be differences in the etiological factors for these two stages of breast cancer. In this cohort, *in situ* diagnoses are largely ductal carcinoma *in situ* (DCIS) which are detected primarily by mammogram, the biological significance of which is not clear. Relative risks (RRs; hazard rate ratios) and 95% confidence intervals (CIs) were estimated using Cox proportional hazards regression models with time-on-study used as the timescale and with age adjusted for linearly within each of two age groups, that is, thus allowing for different slopes for younger (<50 years) and older (≥50 years) women. This approach produced point estimates similar to those observed with the more computationally intense approach of using age as the timescale (*i.e.*, where subjects enter the risk set at the age they filled out the baseline questionnaire and exit at their event/censoring age) with adjustment for birth cohort (calendar time) effects. RRs for alcohol consumption of ≥20 g/day *versus* nondrinkers were of primary interest based on previous findings (4). RRs were adjusted for race/ethnicity (white, nonwhite), daily caloric intake (linearly), a family history of breast cancer in a first degree relative (yes/no), age at menarche (<12, ≥12), nulliparity/age at first full-term pregnancy (FFTP) (nulliparous, FFTP ≤24, 25–29, ≥30), physical activity (hours per week modeled linearly), body mass index (BMI; <25.8, 25.8–32.2, ≥32.3 kg/m^2), and use and duration of estrogen replacement therapy (ERT; none, ≤5 years, >5 years) (12, 13). Note: Hormone replacement therapy (HRT) analyses in Tables 3 and 4 are based on combination HRT; those reported in the text for the duration and timing (current *versus* former) of use are based on ERT use only because this information was not available for progestin use. Effect modification under a multiplicative model was formally assessed using methods described by Walter and Holford (14). Two-sided P values for assessing interaction were based on the term comparing nondrinkers to heavy drinkers (≥20 g/day).

Results

Figure 1 presents a summary of high-risk drinking (≥20 g/day of alcohol) among cohort members at various

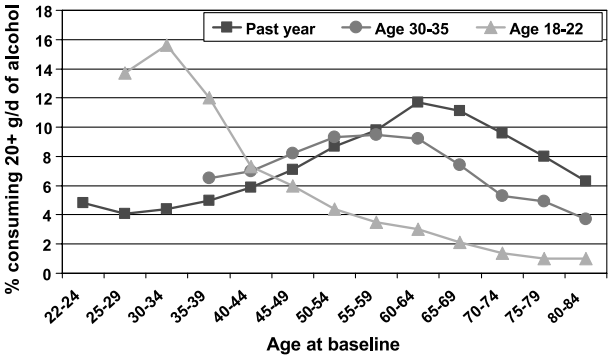

Fig. 1. Percentage of women consuming 20 or more grams of alcohol per day during different periods of life by age at baseline (1995–1996) in the CTS cohort.

periods in their life. Heavy drinking during college (*i.e.*, age 18–22) decreases with age at baseline (which means it increases with calendar year) and is most prevalent among women who were <40 years of age at baseline and in college during the late 1970s and 1980s. Heavy drinking during the mid/late-reproductive years (*i.e.*, age 30–35) was most prevalent among women ages 50–64 at baseline (*i.e.*, among women who were in their mid/late-reproductive years between 1965 and 1975). Women age 60–69 at baseline reported the highest prevalence of high-risk drinking in the preceding year.

Overall, women who consumed ≥20 g/day of alcohol in the year before joining the cohort had a statistically significant increased risk of invasive breast cancer compared to nondrinkers (RR = 1.28, 95% CI: 1.06–1.54). Consumption of <20 g/day did not increase risk. Table 1 presents these data and other age-specific drinking effects by menopausal status defined at the time of joining the cohort. Risk is significantly increased by 32% for recent (*i.e.*, ''past year'' which is the year before joining the cohort) average daily consumption of ≥20 g of alcohol among postmenopausal women. The corresponding increase of 21% in pre/perimenopausal women is not statistically significant but does not differ significantly from that of postmenopausal women (*P* value for interaction = 0.54). Among both pre/peri- and postmenopausal women, moderate drinking at ages 30–35 was associated with some elevation in risk but no dose-response pattern was observed; drinking at ages 18–22 was not associated with risk. When these analyses were repeated using *lifetime* never drinkers (*i.e.*, women reporting no alcohol consumption between ages 18 and 22, 30 and 35, and during the year before joining the cohort) as the referent group, similar patterns were observed with the anticipated elevation in the point estimates. For example, for recent alcohol consumption of ≥20 g/day compared to lifetime never drinkers, RRs were 1.47 (95% CI: 1.15–1.87) for postmenopausal women and 1.39 (95% CI: 0.82–2.36) for pre/perimenopausal women. When change in consumption over time is examined (Table 1), heavy (≥20 g/day) recent consumption is associated with the highest RRs, regardless of previous level of consumption, and women who were previously high consumers but currently consume lower levels or no alcohol are not at significantly elevated risk.

Among postmenopausal women, breast cancer risk was significantly increased among ''daily'' heavy drinkers (*i.e.*, women consuming a weekly average of ≥20 g/day of alcohol and regularly consuming alcohol on 5 or more days per week; Table 2). Only two cases of invasive breast cancer were diagnosed among ''sporadic'' heavy drinkers, making it impossible to determine if risk among this group differed from that among daily heavy drinkers. However, among moderate alcohol consumers (<20 g/day), risk was not associated with drinking pattern.

Among postmenopausal women, we examined modification of the alcohol effects by selected breast cancer risk factors. Table 3 presents subgroup-specific analyses, that is, looking at alcohol consumption within strata of the other variables of interest (where nondrinkers within each strata are treated as the referent group). Table 4 presents these analyses using a common referent group (*i.e.*, nondrinkers in the low-risk strata of the variable of interest). In strata-specific analyses, heavy alcohol consumption often increased risk in subgroups otherwise at low risk of breast cancer (*i.e.*, 42% among women without a family history of breast cancer for ≥20 g/day *versus* nondrinkers; 40% among women with a BMI below 27; and 41% among parous women) but not in subgroups at otherwise elevated risk (*e.g.*, those with a family history of breast cancer, etc.). The exceptions to this observation were for physical activity and women with BBD. Heavy alcohol consumption increased risk similarly in both active and inactive women and women with and without BBD, respectively. For HRT use, risk was increased by 51% for alcohol consumers of ≥20 g/day (relative to nondrinkers) among high-risk women (*i.e.*, those using combination HRT) but not among women who never used HRT. Further examination of the joint effects of alcohol consumption and ERT use showed that alcohol intake of ≥20 g/day (relative to nondrinkers) increased risk among current ERT users (RR = 1.37, 95% CI: 1.07–1.75) but not among former ERT users (RR = 1.08, 95% CI: 0.58–2.02). Among current ERT users, heavy alcohol consumption had similar effects on women who had used estrogen for 5 or fewer years (RR = 1.49, 95% CI: 0.93–2.39) and those who had used it for more than 5 years (RR = 1.34, 95% CI: 1.00–1.80). Women who currently consumed ≥20 g/day of alcohol per day and had used combination HRT had the highest observed RR of over 2-fold compared to nondrinkers who never used HRT; *P* value for interaction = 0.17; Table 4). However, neither this nor any of the other interactions examined in this study were statistically significant.

Discussion

Within this cohort, as well as in most other populations (1–6), average alcohol consumption of two or more drinks per day was associated with a modest increase in invasive breast cancer risk. While increased risk associated with drinking at younger ages cannot be ruled out in our data, recent drinking was most clearly associated with risk. This pattern was apparent when examining the

Table 1. RRs and 95% CIs for invasive breast cancer associated with alcohol consumption at different periods in life, by menopausal status at the time of joining the CTS cohort

Alcohol consumption (g/day)		Pre/perimenopausal women				Postmenopausal women			
		Cases[a]	Person-years	RR[b]	95% CI	Cases	Person-years	RR	95% CI
Past year									
Nondrinkers		95	60,221	1.0		311	65,975	1.0	
<5		53	33,193	0.93	0.66–1.30	181	36,978	1.03	0.86–1.24
5–9		55	33,437	1.05	0.75–1.47	150	30,486	1.04	0.86–1.27
10–14		42	23,776	1.09	0.75–1.57	126	24,500	1.08	0.88–1.33
15–19		27	11,824	1.28	0.83–1.97	82	18,279	0.91	0.71–1.16
≥20		23	10,264	1.21	0.76–1.92	123	19,005	1.32	1.06–1.63
Age 30–35[c]									
Nondrinkers		66	34,936	1.0		249	55,671	1.0	
<5		47	23,994	0.98	0.67–1.43	196	36,036	1.22	1.01–1.47
5–9		67	27,036	1.27	0.90–1.79	177	38,048	1.04	0.84–1.26
10–14		43	18,151	1.23	0.84–1.82	130	23,341	1.28	1.03–1.59
15–19		21	8,985	1.15	0.70–1.89	75	14,383	1.17	0.90–1.51
≥ 20		17	9,085	0.91	0.53–1.57	79	15,060	1.20	0.93–1.55
Age 18–22[d]									
Nondrinkers		112	59,283	1.0		497	97,373	1.0	
<5		54	30,838	0.97	0.70–1.34	171	33,824	1.03	0.86–1.23
5–9		59	30,978	1.12	0.81–1.53	104	25,776	0.85	0.68–1.05
10–14		39	22,192	1.10	0.76–1.60	82	15,250	1.17	0.92–1.48
15–19		9	8,584	0.72	0.37–1.43	25	5,283	1.01	0.68–1.52
≥20		12	15,241	0.62	0.34–1.13	27	5,698	1.07	0.72–1.58
Change in consumption[c]									
Past year	Age 30–35								
None	None	56	30,618	1.0		176	43,108	1.0	
None	<20	25	9,678	1.28	0.79–2.05	93	16,616	1.35	1.05–1.74
<20	None	10	4,167	1.20	0.61–2.35	66	11,703	1.28	0.96–1.70
<20	<20	143	64,818	1.16	0.85–1.59	413	84,613	1.19	0.99–1.42
None/<20	≥20	[e]				45	9,142	1.21	0.87–1.68
≥20	None/<20	10	3,820	1.22	0.62–2.40	79	11,438	1.58	1.21–2.07
≥20	≥20	12	4,165	1.54	0.82–2.90	34	5,918	1.42	0.98–2.06
Change in consumption[d]									
Past year	Age 18–22								
None	None	60	36,805	1.0		224	47,631	1.0	
None	<20	31	18,620	1.11	0.72–1.72	59	13,963	0.96	0.72–1.28
<20	None	47	21,040	1.10	0.75–1.62	236	44,004	1.09	0.91–1.31
<20	<20	115	68,059	1.06	0.77–1.45	257	55,857	1.02	0.85–1.23
None/<20	≥20	10	12,891	0.65	0.33–1.28	18	4,343	1.03	0.63–1.67
≥20	None/<20	20	7,351	1.34	0.80–2.24	103	16,050	1.33	1.05–1.68
≥20	≥20	[e]				9	1,355	1.44	0.74–2.82

[a]Case counts and total person-years reflect women with complete data on all covariates of interest.
[b]Adjusted for age, race/ethnicity, caloric intake, family history of breast cancer, age at menarche, nulliparity/age at FFTP, physical activity, BMI, and duration of ERT use.
[c]Among women >35 years old at baseline.
[d]Among women >22 years old at baseline.
[e]Five or fewer cases.

effects of alcohol at various ages, when either nondrinkers during that period or lifetime nondrinkers were used as the referent group, and when looking at changes in consumption over time. This finding is consistent with some, but not all, previous studies (1, 15–17). Similarly, while not statistically different in the present or some past studies, the effects of alcohol consumption were more consistent and somewhat greater in postmenopausal women than in premenopausal women (2, 3, 15, 17). Whether this observation reflects the lower statistical power among premenopausal women in these studies [due to the overall fewer number of premenopausal women or to temporal changes in drinking patterns resulting in a smaller proportion of recent heavy drinkers among pre/perimenopausal women (see Fig. 1)] or the less detrimental effects of alcohol at younger ages cannot be determined from the available studies.

Drinking patterns, taking into account both quantity and frequency, have not been previously examined to any extent. Tjonneland et al. (8) found that occasional drinkers (who in that study consisted solely of women consuming alcohol on 4 or fewer days per week and less than a weekly average of 20 g/day) were at lower risk (RR = 1.32, 95% CI: 0.67–2.60) than heavy drinkers (those consuming 25–60 g/day; RR = 1.45, 95% CI: 1.10–1.92) but at higher risk than regular moderate (women consuming alcohol on 5 or more days per week with a weekly average of 13–24 g/day) or light (7–12 g/day) drinkers (RR = 1.18, 95% CI: 0.90–1.56 and RR = 0.97, 95% CI: 0.74–1.28, respectively). We were also limited in our ability to assess drinking patterns, but our analyses, even more strongly than those of Tjonneland et al., suggested that it was the amount of alcohol consumed as opposed to the number of days on which it was

Table 2. Association between drinking patterns in the year before baseline and subsequent invasive breast cancer risk among postmenopausal women in the CTS

Drinking pattern[a]	Cases[b]	Person-years	RR[c]	95% CI
Nondrinkers	311	65,975	1.0	
''Sporadic''[d]	282	61,517	0.99	0.84–1.17
''Daily'' <20 g/day	116	22,306	1.07	0.86–1.32
''Daily'' ≥20 g/day	110	16,952	1.34	1.07–1.67

[a]''Sporadic'' drinker defined as consuming alcohol on 4 or less days per week; ''daily'' drinker defined as consuming alcohol on 5 or more days per week.
[b]Case counts and total person-years reflect women with complete data on all covariates of interest.
[c]Adjusted for age, race/ethnicity, caloric intake, family history of breast cancer, age at menarche, nulliparity/age at FFTP, physical activity, BMI, and duration of ERT use.
[d]Only two cases consumed ≥20 g/day of alcohol.

consumed that was important in determining risk. Etiologically, the most interesting comparison would have been between sporadic and daily heavy drinkers but estimation of risk in the former group was not possible due to the very small number of women in that group. Our analyses like those by Tjonneland et al. (8) result in only tentative conclusions about risk group differences.

Limited previous work has also been done in examining host and lifestyle factors which may modify the relationship between alcohol consumption and breast cancer risk (2, 3, 6, 9). As in these previous studies, we found some limited evidence for effect modification. As in the Iowa Women's Health Study (IWHS) (9), we found that the risk associated with alcohol consumption was higher among thin or normal weight women than overweight or obese women. In contrast, the pooled analysis of cohort studies found heavy drinking to increase risk to a greater extent among obese women (2), while the pooled analysis of case-control studies suggested no differences in the magnitude of risk (3). However, in none of these studies were the interactions statistically significant. Similarly, different patterns of risk have been observed for the relationship between a family history of breast cancer, alcohol consumption, and breast cancer risk. We observed the risk associated with heavy drinking (≥20 g/day) to be highest among women without a family history of breast cancer, whereas the pooled analysis of case-control studies found the opposite (3) and the pooled analysis of cohort studies found higher risk associated with alcohol consumption among women with a maternal history of breast cancer but not among women with an affected sister (2). But again, none of these interactions were statistically significant; nor were those between alcohol consumption and a history of benign breast disease (2). In these pooled analyses, however, both premenopausal and postmenopausal women were included despite somewhat stronger (albeit not statistically different) associations between alcohol and risk being observed for postmenopausal women. The extent, if any, to which the inclusion of premenopausal women may have attenuated the risk estimates for interaction effects is not known.

Both HRT and alcohol consumption have been associated with postmenopausal breast cancer risk in the Nurses Health Study (NHS) cohort (6) and alcohol consumption but not ERT in the IWHS cohort (9). Both these cohort studies, as well as our own, have also found an additional elevation in risk among women having both these exposures; however, only in the IWHS and an early report from the NHS were these interactions statistically significant on a multiplicative scale. Nonetheless, the consistency of these findings is notable. Compared to nondrinkers who have never used HRT, heavy drinkers (*i.e.*, ≥15 g/day in the IWHS and ≥20 g/day

Table 3. Associations[a] between recent alcohol consumption and postmenopausal breast cancer among selected subgroups in the CTS

Subgroup	Alcohol consumption		
	Nondrinkers	<20 g/day	≥20 g/day
No family history of breast cancer	1.0 [246]	1.04 (0.89–1.22) [433]	1.42 (1.13–1.79) [105]
Breast cancer in a first degree relative	1.0 [65]	0.94 (0.69–1.29) [106]	0.92 (0.54–1.57) [18]
BMI < 27.3 (normal or only marginally overweight)	1.0 [195]	1.09 (0.92–1.30) [404]	1.40 (1.09–1.79) [99]
BMI ≥ 27.3 (overweight or obese)	1.0 [116]	0.88 (0.69–1.13) [135]	1.10 (0.71–1.72) [24]
Parous	1.0 [239]	1.10 (0.94–1.29) [443]	1.41 (1.11–1.80) [95]
Nulliparous	1.0 [72]	0.77 (0.56–1.04) [96]	1.02 (0.65–1.59) [28]
Physically active[b]	1.0 [167]	1.09 (0.91–1.32) [365]	1.33 (1.02–1.74) [81]
Not physically active	1.0 [144]	0.93 (0.75–1.17) [174]	1.34 (0.95–1.90) [42]
No history of benign breast disease (BBD)	1.0 [228]	1.01 (0.85–1.19) [384]	1.26 (0.99–1.64) [85]
Biopsy indicating BBD	1.0 [83]	1.07 (0.82–1.40) [155]	1.44 (0.97–2.13) [38]
No HRT	1.0 [68]	0.99 (0.72–1.37) [87]	0.98 (0.55–1.73) [15]
Estrogen only	1.0 [98]	0.98 (0.76–1.27) [157]	1.24 (0.84–1.84) [36]
Estrogen plus progestin	1.0 [130]	1.09 (0.88–1.35) [282]	1.51 (1.13–2.03) [70]

[a]RR (95% CI) and [number of breast cancer cases with complete data on all covariates of interest]; adjusted for age, race/ethnicity, caloric intake, age at menarche, family history of breast cancer, BMI, nulliparity/age at FFTP, physical activity, and duration of ERT use.
[b]Defined as 1.5 or more hours per week of strenuous or moderate exercise during the past 3 years.

Table 4. Joint associations[a] between recent alcohol consumption and other risk factors for postmenopausal breast cancer in the CTS

	Alcohol consumption		
	Nondrinkers	<20 g/day	≥20 g/day
Family history of breast cancer in a first degree relative			
No	1.0	1.04 (0.89–1.22)	1.44 (1.14–1.81)
Yes	1.63 (1.24–2.15)	1.56 (1.24–1.96)	1.44 (0.89–2.33)
BMI (kg/m^2)			
<27.3	1.0	1.10 (0.93–1.31)	1.41 (1.10–1.80)
≥27.3	1.21 (0.96–1.53)	1.06 (0.85–1.32)	1.33 (0.87–2.04)
Parous	1.0	1.10 (0.94–1.29)	1.40 (1.10–1.78)
Nulliparous	1.26 (0.97–1.64)	0.99 (0.78–1.25)	1.31 (0.89–1.94)
Physically active[b]			
Yes	1.0	1.09 (0.91–1.31)	1.32 (1.01–1.72)
No	1.12 (0.89–1.40)	1.05 (0.85–1.30)	1.53 (1.09–2.15)
Biopsy-diagnosed BBD			
No	1.0	1.00 (0.85–1.19)	1.26 (0.98–1.63)
Yes	1.35 (1.05–1.73)	1.46 (1.19–1.79)	1.97 (1.39–2.79)
Use of HRT			
Never	1.0	1.00 (0.72–1.37)	0.94 (0.54–1.65)
Estrogen only	1.18 (0.87–1.60)	1.17 (0.88–1.56)	1.54 (1.04–2.30)
Estrogen plus progestin	1.53 (1.14–2.05)	1.63 (1.25–2.14)	2.24 (1.59–3.14)

[a]RR (95% CI) adjusted for age, race/ethnicity, caloric intake, age at menarche, and except in models with these factors as main effects, for a family history of breast cancer, BMI, nulliparity/age at FFTP, physical activity, and duration of ERT use.
[b]Defined as 1.5 or more hours per week of strenuous or moderate exercise during the past 3 years.

in the NHS and the CTS) who have used HRT (''ever use of ERT'' in the IWHS, current ERT/HRT use for >5 years in the NHS, and for ''ever'' use of combination HRT and for current use of ERT for >5 years in the CTS) are at approximately twice the risk of developing invasive breast cancer (RR = 1.83, 95% CI: 1.18–2.85 in the IWHS; RR = 1.99, 95% CI: 1.41–2.79 in the NHS; and RR = 2.24, 95% CI: 1.59–3.14 and RR = 2.20, 95% CI: 1.57–3.08, respectively, in the present study). Contrary to these findings, risk associated with a 10 g/day increase in alcohol consumption was similar for never, past, and current ERT/HRT users in Denmark (8) and in the pooled analysis of both cohort and case-control studies (2, 3). Thus, on balance, it is unclear whether the risk associated with the combination of heavy drinking and ERT/HRT use is synergistic or additive.

Age-adjusted breast cancer incidence rates in the CTS cohort are more than 50% higher than other white, non-Hispanic California women (11). A similar pattern is seen among women living in Marin County, CA, an area, like Long Island, NY, where high breast cancer rates are currently of substantial concern to residents (18). Both the CTS cohort and Marin County residents have particularly high exposure to both HRT and alcohol [ever use of HRT: 74% in the CTS and 71% in Marin County (19) *versus* 52% in other California women; and 10% of the CTS cohort consuming ≥20 g/day of alcohol in 1995–1996 and 27% of Marin County women consuming ≥2 drinks per day in 1997–1999 *versus* 7% of the NHS cohort consuming ≥20 g/day of alcohol in 1994]. The established relationship between each of these factors and invasive breast cancer risk and the possible synergy between these two exposures suggests that limiting alcohol consumption to moderate amounts (*i.e.*, an average of less than two drinks per day) and refraining from the use of HRT may reduce invasive breast cancer rates in these and other similarly high-risk populations.

While recall biases are likely to be low in cohort studies assessing alcohol exposure before cancer diagnosis, a potential limitation of our study, as with virtually all dietary and alcohol assessments that rely on using food-frequency questionnaires to assess intake, is the possibility of misclassification of exposure due to inaccuracies in reporting. We are in the process of conducting a reliability and validation/calibration study within the CTS cohort. Preliminary analyses of alcohol effects suggest a reasonably reliable and valid alcohol assessment for the ''past year'' period was obtained using the food-frequency questionnaire method compared to four 24-h recalls and that adjusting the overall alcohol effect for misclassification does not impact overall conclusions. However, we were not able to assess the reliability or validity of self-reports of alcohol consumption at younger ages. Thus, measurement error remains a possible explanation for the lack of association between drinking during earlier periods of life and subsequent breast cancer risk.

In summary, our findings suggest that recent alcohol consumption probably plays a larger role in invasive breast cancer risk than does consumption at earlier ages and that the average quantity of alcohol consumed is more important than the relative frequency with which it is consumed. The examination of host and lifestyle factors suggests that, with the exception of benign breast disease and HRT use, women who are otherwise at

higher risk for postmenopausal breast cancer (*e.g.*, women with a family history of breast cancer) may not accrue much additional risk with heavy alcohol consumption. An important exception to this observation may be the use of HRT where there is a consistent suggestion (albeit, a statistically nonsignificant interaction) in the CTS as well as in two other cohort studies that invasive breast cancer risk is highest among women exposed to both these factors. This combination of exposures may well play a role in the higher breast cancer incidence rates observed in certain populations and should be investigated further. Further investigation into the effects of genetic variation in the metabolism of alcohol and steroid hormones also may prove promising in elucidating the nature of these individual and joint relationships.

Acknowledgments

We thank Jane Sullivan-Halley for her work in preparing a number of the covariates used in this analysis and Orawan Takaki for administrative support.

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Cancer Epidemiol Biomarkers Prev 2004;13:405-411.