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Wine, liquor, beer and risk of breast cancer in a large population ☆

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ABSTRACT

Population studies show a relation of alcohol drinking to an increased risk of breast cancer (BrCa). Aiming to investigate uncertainties about a risk threshold, the role of beverage type and interactions with other BrCa predictors, we performed a cohort study among 70,033 women, 2829 of whom developed BrCa. Using Cox proportional hazards models with 8 covariates, the following relative risks (95% confidence intervals) for BrCa versus lifelong abstainers were found: 1.08 (0.95–1.22) at <1 drink per day, 1.21 (1.05–1.40, $p = 0.01$) at 1–2 drinks daily and 1.38 (1.13–1.68, $p = 0.002$) at ⩾3 drinks daily. Increased BrCa risk was concentrated in women with oestrogen receptor positive tumours with no major disparity related to choice of wine, liquor, beer or type of wine (red, white, etc). We conclude that with a threshold below 1–2 drinks daily, a hormone-related mechanism mediates a relation of alcohol drinking to an increased BrCa risk.

1. Introduction

Most published studies show an increased risk of female breast cancer (BrCa) among women who drink alcoholic beverages.[1–8] A World Cancer Fund report[8] stated 'there is ample, generally consistent evidence from case-control and cohort studies.' Suspicion aroused by geographic variation in BrCa incidence has led investigators to scrutinise possible modifiable environmental risk factors. A recent reviewer[9] stated that prospective epidemiologic studies showed 'no association that is consistent, strong, and statistically significant, with the exception of alcohol intake, overweight, and weight gain'.

While the BrCa relation is clearest at heavier alcohol intake (⩾3 standard-sized drinks per day), such drinking is relatively uncommon in women and is a well-known factor in many medical and social problems. The less clearly established relation between lighter drinking and BrCa is a more important public health issue. Need remains for an estimate of a reasonably safe or sensible limit of drinking for women with respect to BrCa risk. Other unresolved aspects include the role of beverage choice (wine, liquor or beer), relations of alcohol to stage at diagnosis and possible interactions with ethnicity, menopausal status, hormone treatment and hormone receptor status. Hoping to cast light upon several of these aspects, we

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extended a reported cohort study of alcohol relations in 303 BrCa subjects[10], and report here the data of 2829 women.

2. Patients and methods

2.1. Study population and data

Study protocols were approved by the Institutional Review Board of the Kaiser Permanente Medical Care Programme. Baseline data were from questionnaires at health examinations in 1978–1985. The examinees were a multi-ethnic cohort of 70,033 women (mean baseline age = 40.6 years) free of BrCa history, who were members of a comprehensive pre-paid health care programme in the San Francisco Bay Area. Usually taken as a voluntary routine health appraisal, the examination[11] included health measurements, self-classified ethnicity and queries about socio-demographic status, habits, medical history and symptoms. Data about the women's alcohol consumption were supplied during the examination on check-sheet questionnaires. The study cohort comprised 79.8% of all examinees; the remainder included persons who took the examination during absences of a special research clerk and persons who declined, largely because of the lack of fluency in English.

Lifelong abstainers were defined as the persons who reported drinking no alcohol during the past year and 'never or almost never' before the past year. Ex-drinkers were non-drinkers during the previous year who indicated prior alcohol drinking. Current drinkers checked usual drinking as less than 1 drink per month ('special occasions only'), more than 1 per month but less than 1 drink per day and as daily number of drinks, 1–2, 3–5, 6–8 and ⩾9 per day. Drinkers received separate questions about the number of days per week they drank wine, liquor or beer, and they were asked to write in 'type of wine'. Wine, liquor or beer 'preponderance' was defined among women reporting >1 drink per month as an exclusive intake of the type or drinking the type more often than the other two. If a woman reported more than one type with equal frequency preponderance was defined as 'none'. Data from a subset in 1984–1985 showed a good correlation of frequency to the number of drinks per week of the beverage type, with an average of 80–90% of beverage alcohol taken as the preponderant type.[12]

2.2. BrCa subjects

BrCa occurrence was ascertained through the Health Care Programme's Cancer Registry, which covers all subscribers and contributes to the local surveillance, epidemiology and end results (SEER) programme.[13] Table 1 presents the data about the study population and BrCa subjects. Deaths were ascertained from California vital statistics records.

2.3. Analytic methods

Subjects were followed until 31st December 2004, BrCa diagnosis or termination of health plan membership. Mean follow-up was 16.0 years, yielding an estimated 1,120,528 person-years of follow-up. Age-adjusted and multivariate models used the Cox proportional hazards model. Covariates were age (continuous), ethnicity (white referent, black, Asian, Hispanic, others), education (no college referent, some college, college graduate), body mass index (<25 kg/m^2 referent, 25–29 kg/m^2, ⩾30 kg/m^2), marital status (married referent, never married, formerly married), cigarette smoking (never smoked referent, ex-smoker, <1 pack per day, ⩾1 pack per day), 'childless or first child at >35 years' (yes/no), history of any breast surgery (yes/no) and 'mother/sister BrCa' (yes/no).

Total alcohol was studied categorically in most models, with lifelong abstainers as referent and 5 other categories (ex-drinkers, <1 per month, >1 per month but <1 drink/day, 1–2 drinks/day, ⩾3 drinks per day). Excluding ex-drinkers, trend tests were done with the same covariates and drinking category number as an ordinal variable. We also performed another analysis exclusive of ex-drinkers with the total alcohol as a continuous variable, assigning daily number of drinks to individuals as 0.03 for <1/month, 0.5 for >1 per month but <1/day, 1.5 for 1–2 per day and 4.5 for ⩾3 per day.

Several strata were studied by the similar methods, including women with cancers classified as oestrogen receptor (ER)

Table 1 – Selected traits of study cohort and breast cancer subjects.

Trait	Cohort		Breast cancer	
	n	Percent	*n*	Percent
Total	70,033	100	2829	100
Ethnicity				
Black	20,698	30	744	26
White	3708	53	1671	59
Asian	7500	11	280	10
Hispanic	3118	4	98	3
Other	1633	2	46	2
Age at examination				
Age <50	50,206	78	1399	49
Age ⩾50	19,827	22	130	51
Total alcohol drinking[a]				
Never	10,961	16	442	16
Ex-drinker	1718	2	81	3
<1 drink/month	18,627	27	761	27
>1/mo; <1/day	25,477	36	896	32
1–2 drinks/day	9532	14	466	16
⩾3 drinks/day	2870	4	147	5
Beverage type preponderance[b]				
Wine[a]	10,570	15	476	17
Liquor[a]	3783	5	219	8
Beer[a]	2702	4	84	2
None[a]	20,824	30	730	26
Beverage type taken ⩾2 days per week				
Wine	14,632	21	661	23
Liquor	7753	11	427	15
Beer	5246	7	172	6

None indicates reported more than one type with equal frequency.
a There were 848 women with incomplete data about drinking amount; because of this and rounding, percentages do not always add to 100%.
b Beverage 'preponderance' was defined as an exclusive intake or drinking the type more often than either of the other two. This was determined among women reporting >1 drink per month; percentages in the table represent all women.

and progesterone receptor (PR) positive and negative. From 1996 on, all tests were performed in the Kaiser Permanente immunohistochemistry laboratory, which considered a test positive if ⩾5% of nuclei were positively stained.

Beverage choice was studied among women reporting more than one drink per month in two ways. (a) A continuous variable was derived from the number of days per week each type was taken, as follows: never/almost = 0.0; ⩽once per week = 0.5, 2–3 days = 2.5, 4–5 days = 4.5 and daily/almost = 6.5; this was entered as a covariate in the multivariate models. Similar modelling was performed with the subsets of wine types (red table wine only, white table wine only, red and white table wine only and other wine). (b) Risk of BrCa was compared in beverage preponderance groups with 'none' as referent for wine, liquor and beer groups.

To screen for possible underestimation of drinking among persons reporting <3 drinks/day, we included in some models a 'possible under-reporter' variable. Determined from persons with ⩾2 examinations, this category represents persons judged by an inference more likely to be under-estimators because they stated heavy intake on another occasion or because they received at any time an in-patient or out-patient diagnosis of an alcohol-related condition. This process is described in detail elsewhere.[14]

We report relative risks, 95% confidence intervals and associated *p* values.

3. Results

3.1. Total alcohol and BrCa risk

In fully adjusted models, the relative risks (RRs) and 95% confidence intervals (CIs) for BrCa versus lifelong abstainers were 1.08 (0.95–1.22) at <1 drink per day, 1.21 (1.05–1.40, $p = 0.01$) at 1–2 drinks daily and 1.38 (1.13–1.68, $p = 0.002$) at ⩾3 drinks daily (Table 2). These relations were generally similar in most stratified groups. While they appeared weaker in groups younger at baseline or at BrCa diagnosis and in African American women (Table 3), the 95% CI for these strata overlapped those of the others. The test for trend was significant with a *p* value of 0.002. The model with alcohol as a continuous variable yielded a RR per drink per day of 1.05 (1.01–1.10, $p = 0.008$).

3.2. Beverage choice and BrCa risk

Analyses controlled simultaneously for frequency (per day per week) of drinking major beverage types (Table 4) showed little relation of any type to BrCa risk. With wine frequency

Table 2 – Adjusted[d] relative risk of breast cancer by alcohol and other selected traits.

Group	N BrCa	Relative risk (95% CI)	
		Age-adjusted	Multivariate[d]
Alcohol intake (versus 442 never drinkers with breast cancer)			
Ex-drinker	82	1.3 (1.0–1.6)[a]	1.2 (1.0–1.5)
<1 drink per month	761	1.1 (1.0–1.6)[a]	1.1 (1.0–1.3)
<1 drink per day	896	1.1 (1.0–1.3)[a]	1.1 (1.0–1.2)
1–2 drinks per day	466	1.3 (1.2–1.5)[c]	1.2 (1.1–1.4)[a]
⩾3 drinks per day	147	1.5 (1.3–1.9)[c]	1.4 (1.1–1.7)[b]
Ethnicity (versus 1671 white women with breast cancer)			
African American	744	0.8 (0.7–0.8)[c]	0.9 (0.8–1.0)
Asian–American	270	0.9 (0.8–1.0)	1.0 (0.9–1.2)
Other	46	0.8 (0.6–1.0)	0.9 (0.6–1.1)
Hispanic	98	0.8 (0.6–0.9)[b]	0.9 (0.7–1.1)
Smoking (versus 1440 never smokers with breast cancer)			
Ex-smoker	613	1.2 (1.1–1.3)[c]	1.1 (1.0–1.3)[a]
Smoke <1 pack per day	435	1.1 (1.0–1.2)	1.1 (1.0–1.2)
Smoke ⩾1 pack per day	234	1.3 (1.1–1.5)[c]	1.3 (1.1–1.5)[b]
Other selected covariates			
Body mass index ⩾30 kg/m^2 (versus 1665 with BMI <25 kg/m^2)	442	1.5 (1.4–1.7)[c]	1.5 (1.4–1.7)[c]
College graduate (versus 1134 with no college)	281	1.5 (1.2–1.7)[c]	1.5 (1.2–1.7)[c]
Never married (versus 1520 married)	665	1.1 (1.0–1.2)[b]	1.1 (1.0–1.2)[a]
History of breast surgery (versus 2387 without history)	442	1.5 (1.4–1.7)[c]	1.5 (1.4–1.7)[c]
Mother or sister with breast cancer (versus 2548 'no')	281	1.5 (1.2–1.7)[c]	1.5 (1.2–1.7)[c]
Childless or first child at >35 years (versus 2164 'no')	665		1.1 (1.0–1.2)[a]

a $p < 0.05$.
b $p < 0.01$.
c $p < 0.001$.
d Cox proportional hazards model with age, ethnicity, education, body mass index, marital status, smoking alcohol, history of any breast surgery, family history and parity; numbers do not add up to 2829 total breast cancer because of the missing values in models BMI = body mass index

Table 3 – Adjusted[a] relative risk of breast cancer by alcohol in selected groups.[b]

Group	N with cancer	Relative risk (95% confidence interval) versus never drinkers (referent)		
		<1 drink per day	1–2 drinks per day	>3 drinks per day
All	2,829	1.1 (0.95–1.2)	1.2 (1.1–1.4)[c]	1.4 (1.2–1.6)[d]
Ethnicity				
White	1,671	1.2 (0.99–1.5)	1.3 (1.1–1.6)[c]	1.5 (1.2–2.0)[d]
Black	744	0.9 (0.8–1.2)	1.2 (0.9–1.6)	1.1 (0.7–1.7)
Asian	270	1.0 (0.6–1.4)	1.3 (0.8–2.4)	3.5 (1.4–8.8)[d]
Hispanic	87	1.0 (0.601.9)	1.4 (0.7–3.0)	0.9 (0.7–1.1)
Baseline age				
<50 years	1399	1.0 (0.9–1.3)	1.2 (0.9–1.4)	1.1 (0.8–1.5)
⩾50 years	1430	1.1 (0.9–1.2)	1.1 (0.9–1.3)	1.4 (1.1–1.9)[d]
Age at diagnosis				
<55 years	818	1.1 (0.9–1.4)	1.2 (0.9–1.6)	1.1 (0.7–1.7)
⩾55 years	2011	1.0 (0.9–1.2)	1.1 (0.9–1.3	1.4 (1.1–1.7)[d]
Baseline smoking status				
Never smoked	1,440	1.0 (0.9–1.2)	1.1 (0.9–1.3)	1.5 (1.0–2.1)[c]
Ex-smoker	613	1.3 (0.9–1.9)	1.3 (0.9–2.0)	1.7 (1.1–2.7)[c]
<1 pack per day	435	1.1 (0.8–1.7)	1.4 (0.9–2.2)	1.3 (0.8–2.3)
⩾1 pack per day	234	1.5 (0.7–3.2)	1.8 (0.8–4.1)	1.7 (0.8–4.0)
Stage at diagnosis				
In situ	433	1.1 (0.8–1.5)	1.5 (1.0–2.1)[c]	1.4 (0.8–2.4)
Local	1589	1.1 (0.9–1.3)	1.2 (1.0–1.4)	1.3 (1.0–1.7)[c]
Regional/metastatic	807	1.1 (0.9–1.4)	1.2 (0.9–1.5)	1.4 (1.0–2.1)
Interval between baseline examination and breast cancer diagnosis				
<5 years	439	1.3 (0.9–1.7)	1.4 (1.0–2.0)	1.3 (0.8–2.2)
5–9 years	555	1.1 (0.8–1.3)	1.2 (0.9–1.6)	1.2 (0.8–1.9)
10–14 years	602	1.2 (0.9–1.6)	1.3 (1.0–1.8)	1.6 (1.0–2.4)[c]
⩾15 years	1233	1.0 (0.8–1.2)	1.2 (0.9–1.4)	1.5 (1.1–1.9)[c]
Vital status				
Died of BrCa	288	0.8 (0.5–1.1)	0.9 (0.5–1.4)	1.2 (0.6–2.3)
Died other cause	538	1.1 (0.8–1.5)	1.3 (1.0–1.4)[c]	1.4 (0.9–2.1)
Known alive	1815	1.0 (0.9–1.2)	1.2 (1.0–1.6)	1.3 (1.0–1.6)

a Separate Cox proportional hazards models for each group. Models include age, ethnicity, education, body mass index, marital status, smoking alcohol, history of any breast surgery, family history and parity.
b Lifelong abstainers are referent. Exdrinkers and infrequent drinkers (< 1 drink per month) were in the models, but data for these categories are not shown.
c $p < 0.05$.
d $p < 0.01$.

Table 4 – Adjusted[a] relative risk breast cancer according to frequency of drinking wine, liquor and beer.

Relative risk (95% CI) of wine, liquor and beer per day per week[b]		
Wine	Liquor	Beer
1.02 (0.99–1.04)	1.01 (0.98–1.04)	1.01 (0.97–1.06)

CI = confidence interval.
a Among daily drinkers by Cox model controlled age, ethnicity, education, body mass index, marital status, smoking alcohol, history of any breast surgery, family history, parity, total n drinks and other beverage types.
b Continuous variable for usual frequency of each beverage type; see text for further definition. RR's represent estimates of independent risk per day per week.

subdivided (red, white, etc.), no specific wine type was related to risk (data not shown).

In models comparing the wine, liquor and beer preponderance groups to one another (not in tables) there was little independent relationship to BrCa risk. For example, compared to drinkers with no preponderant beverage type, the RR (CI)'s for other preponderance groups were 1.06 (0.94–1.20) for wine, 1.02 (0.87–1.21) for liquor and 1.02 (0.81–1.29) for beer.

3.3. *Hormone receptor status and the alcohol–BrCa relationship*

The alcohol relation was similar for ER positive tumours whether or not the cancers were PR positive (Table 5). In women with ER negative tumours there was no alcohol–BrCa relationship, irrespective of PR status, and the relationship was intermediate when ER status was unknown. The 25 women with

Table 5 – Adjusted[c] RR (CI) breast cancer by alcohol stratified by hormone receptor status.

Oestrogen/progesterone receptor status	N BrCa	RR (95% CI) versus never drinkers (referent)		
		<1 drink per day	1–2 drinks per day	⩾3 drinks per day
Oestrogen positive	1019	1.1 (0.9–1.4)	1.4 (1.1–1.7)[a]	1.7 (1.2–2.3)[b]
Oestrogen negative	268	1.1 (0.7–1.6)	0.8 (0.5–1.3)	0.8 (0.3–1.8)
Oestrogen unknown	1542	1.1 (0.9–1.3)	1.2 (1.0–1.5)[a]	1.3 (1.0–1.7)[a]
Progesterone positive	808	1.1 (0.9–1.4)	1.2 (0.9–1.6)	1.6 (1.1–2.3)[b]
Progesterone negative	446	1.1 (0.8–1.6)	1.2 (0.8–1.8)	1.2 (0.7–2.1)
Progesterone unknown	1575	1.1 (0.8–1.6)	1.2 (0.8–1.8)	1.2 (0.7–2.1)
Both positive	782	1.2 (0.9–1.5)	1.3 (1.0–1.7)	1.7 (1.2–2.5)[b]
Both negative	236	1.1 (0.7–1.6)	0.9 (0.5–1.6)	0.7 (0.3–1.8)
Oestrogen positive–progesterone negative	207	1.1 (0.7–1.7)	1.6 (0.9–2.6)	1.7 (0.9–3.4)
Progesterone positive– oestrogen negative	26	0.2 (0.1–1.0)	–	0.7 (0.1–6.5)
Both unknown	1539	1.1 (0.9–1.3)	1.2 (1.0–1.5)[a]	1.3 (1.0–1.7)[a]

RR = relative risk, CI = confidence interval.
a $p < 0.05$.
b $p < 0.01$.
c Cox proportional hazards models with age, ethnicity, education, body mass index, marital status, smoking alcohol, history of any breast surgery, family history and parity.

tumours positive for progesterone but negative for oestrogen receptor status seemed too few for useful estimates.

3.4. *BrCa risk according to inferred likelihood of under-estimation*

Compared to women reporting never drinking on ⩾2 occasions and with no alcohol-related diagnoses, the RR (CI)'s for women reporting <1 drink per month were 1.08 (0.92–1.29; $p = 0.3$) for unlikely under-estimators and 1.23 (0.96–1.57; $p = 0.1$) for more likely under-estimators. For women reporting >1 drink per month but <1 per day, these RR's were 1.03 (0.82–1.23; $p = 0.8$) for unlikely under-estimators and 1.33 (1.06–1.65; $p = 0.01$) for more likely under-estimators. For the subgroups of women reporting 1–2 drinks per day, the RR's were 1.21 (1.00–1.47; $p = 0.06$) for unlikely under-estimators and 1.24 (10.99–1.54; $p = 0.06$) for more likely under-estimators.

3.5. *Ethnicity, cigarette smoking and other covariates*

While there was no major overall difference in BrCa risk between black and white women (Table 2), there was a disparity within age strata; e.g. black/white RR (CI) for BrCa diagnosed at age <55 years = 1.2 (1.0–1.4, $p = 0.08$) and at age ⩾55 years = 0.8 (0.7–0.9, $p < 0.001$). There were no major black/white differences in the risk of *in situ* diagnosis (RR = 1.1 [0.9–1.5]) or of nodal/distal spread at diagnosis (RR = 1.0 [0.8 = 1.2]). Black women were more likely to suffer death attributed to BrCa (RR = 1.3 [1.0–1.8, $p = 0.04$]).

There was no Asian/white difference in BrCa risk (Table 2), nor was there a disparity between specific Asian ethnic subsets (Chinese, Japanese, Filipino, etc) and whites (data not shown). *In situ* BrCa diagnosis was more likely among Asian women than among whites (RR = 1.4 [1.0–2.0, $p = 0.03$]). The Asian/white RR of BrCa with nodal/distal spread at diagnosis was 0.8 (0.6–1.1, $p = 0.2$).

Independent of alcohol consumption, cigarette smoking was weakly related to BrCa risk (Table 2), but this was not consistent in subsets. For example, among never drinkers RR = 0.9 (0.4–2.0) and among college graduates RR = 1.0 (0.8–1.4). Adiposity, higher educational attainment, prior breast surgery, family BrCa history and nulliparity or late first pregnancy were, as expected, all related to an increased BrCa risk.

4. Discussion

4.1. *Total alcohol and BrCa risk*

This study confirms an increased risk of BrCa among women reporting daily drinking.[1–8] The relation is supported by a progressive increase in risk from 1–2 drinks to ⩾3 drinks per day and by consistency in most strata. Among women reporting <1 drink per day there was an increased BrCa risk among those suspected of under-reporting, but no such relation among the remainder. This suggests a risk threshold somewhere in the broad 1–2 drinks/day category, but exactly where cannot be determined.

Individual previous reports differ about whether the alcohol–BrCa relation is linear or has a threshold. Meta-analyses and pooled studies often examine alcohol as a continuous variable, which usually produces estimates indicating a linear relation to BrCa. One meta-analysis of 38 case-control and cohort studies[2] showed an increased BrCa risk of 11%, 24% and 38% at 1, 2 and 3 drinks per day. Another reviewer[5] concluded that there was a 'dose-response relationship beginning with intakes 'as low as 1–2 drinks per day'. A pooled analysis of 7 cohort studies[3] showed that at intakes of <60 g per day 'risk increased linearly with RR of 1.09 per 10 g of alcohol per day'. A meta-analysis of 58,515 women from 53 studies[7] showed an increased BrCa risk of 7% per 10 g in all studies, with 5% per 10 g per day among 9693 women in prospective studies. A large ($n = 4285$) multi-centre study[15] reported a 3%

increased risk per 10 g of alcohol per day with alcohol entered as a continuous variable. In that study[15] with alcohol studied categorically, the RR was 0.97 (0.88–1.08) at 4.7–10 g, alcohol per day, suggesting a threshold above that intake.

Using categorical modelling of intake, we found a risk threshold, but with alcohol as a continuous variable we obtained an estimated 5% increased per drink per day. Alcohol relations to chronic conditions are generally non-linear, including several U-shaped and J-shaped curves. Thus, we have preferred categorical modelling for the estimation of possible thresholds. Even in analyses employing categories, there is a strong likelihood of spurious lowering of apparent thresholds due to under-reporting.[14]

4.2. *Beverage choice and BrCa risk*

Study of the independent role of beverage choice is difficult because only a minority of persons in our study population reported only one beverage type[12] and because of probable residual confounding by user traits.[12,16] The beverage choice aspect has implications with respect to mechanisms, because an independent association would imply mechanisms for risk other than for an alcohol effect.

We interpret our beverage choice data as showing no independent relation of any major (wine, liquor or beer) beverage type or of type of wine. Probably, the better evidence for this is the model with the data about the frequency of beverage types, because it affords simultaneous comparison. The preponderance group comparisons are more susceptible to confounding by user traits in these selected sets of drinkers,[12] yet the model showed no important differences.

4.3. *Hormone receptor sensitivity status*

Our data show an alcohol–BrCa relation only among women with ER positive BrCa. Date of diagnosis was the only major selection factor for the determination of hormone receptor status. Thus, there is a hypothetical bias related to alcohol habits because longer intervals between determination of drinking habit and BrCa allow a greater possibility of change in usual drinking. The most common change with an increasing age is less intake,[17] making such bias likely to move the alcohol–BrCa relation towards null. This consideration strengthens the likelihood that the alcohol-receptor status relations are valid.

Previous reports about the interactions of alcohol and hormone receptor status are conflicting. In a 2004 review, largely of case-control analyses[18] it was concluded that 'risks associated with—alcohol consumption did not differ by receptor status'. A prospective analysis from the Iowa Women's Health Study[19] reported that an increased BrCa risk among alcohol drinkers was essentially limited to ER negative tumours. In the Nurses Health Study cohort[20] alcohol use before menopause was more strongly associated with the incidence of ER positive/PR positive+ tumours than with ER negative/PR negative tumours but the difference was not statistically significant. Similar heterogeneity was seen in the data from the Ontario Cancer Registry.[21] The Swedish Mammography Cohort[22] found an increased risk only for ER positive tumours. Recent reviewers remarked that large subgroups and a wide range of alcohol intake categories are needed to study this area, and that, with these conditions, a strong alcohol relation is seen only for oestrogen receptor positive tumours.[23] Our data fit these conditions and results.

4.4. *Possible mechanisms*

An effect via a sex hormonal path is the leading hypothetical explanation for the increased BrCa risk of alcohol drinkers.[2–8] Cumulative lifetime exposure to estradiol has been hypothesised as a BrCa risk factor, and alcohol has been reported to contribute to increased estradiol blood levels in both premenopausal and post-menopausal women.[5] With respect to estradiol and other hormones, various reports show increased endogenous production, decreased clearance or both.[22] Alcohol may increase the expression of oestrogen receptors,[24] thus stimulating the proliferation primarily of oestrogen receptor positive cells.

Alcohol might influence BrCa by other hypothetical pathways.[23,25] While not thought to be a direct mutagenic carcinogen, alcohol might act as a promoter or facilitator of other cancer-inducing substances. Since alcohol-metabolising enzymes are present in human breast tissue, alcohol's metabolite, acetaldehyde, a known weak mutagen, could be carcinogenic. Reactive oxygen species, resulting from ethanol metabolism, may be involved in breast carcinogenesis by causing damage, as well as by generating DNA and protein adducts. These could act directly via oxidative damage and/or by affecting folate and one-carbon metabolism pathways. Alcohol can negatively affect folate levels,[26] thus affecting DNA methylation and DNA synthesis, which play a role in carcinogenesis. We have no data about folate intake or blood levels. Genetic polymorphisms might play a role in all these potential pathways.

4.5. *Ethnicity, smoking and other covariates*

Disparities in this analysis between white and black women were modest. The greater BrCa likelihood at younger ages and higher mortality among black women had been reported previously.[27] The similar black/white proportions *in situ* BrCa make it unlikely that disparity in access to care was an important factor in this prepaid health care plan. It has been reported that women enrolled in health maintenance organisations receive earlier BrCa diagnoses, than those receiving fee-for-service care.[28]

The data about Asian American women also indicate no Asian/white disparity in access to care. In fact, the higher proportion of *in situ* diagnoses suggests that Asian women now avail themselves of mammography more than white women, a change from the previously reported under-use of BrCa screening by Asian Americans.[29] Apparently, acculturation in this Northern California population has eliminated disparities in BrCa risk previously noted between Asian and white women and, perhaps between different Asian American ethnic groups.[29]

Our data suggest a weak independent relation of smoking to BrCa, but inconsistencies were noted. Given the correlation between smoking and alcohol drinking, residual confounding by the latter is possible, as has been suggested.[30]

The relationships to age, BMI, education, parity, family history and prior breast surgery were all as expected.

4.6. Limitations

Determination of habits only at baseline is a limitation, but there is a known relative stability of drinking amount and beverage preference in this population,[12,17] and relations of alcohol consumption to BrCa risk were as strong in the later years of follow-up as in the earlier years. A second limitation is the lack of precise data about the proportions of alcohol taken as the specific beverage and wine types in individuals, but women in 'red only' and 'white only' categories represent clearly defined groups that showed quite similar BrCa risks. A third limitation is the inability to control for some traits with probable relationships to alcohol habits; these include dietary habits, physical exercise and vitamin/antioxidant supplement use. Incomplete follow-up of all examinees could be a limitation if this were systematically related to alcohol habits, an unlikely possibility. Finally, like all reported analyses of alcohol intake and BrCa, this study is observational. Only a controlled clinical trial, unlikely to be performed for the alcohol–BrCa relation, might account completely for all confounders.

4.7. Public health considerations

Consideration of overall risks of alcohol drinking in women needs to account for individual risk/benefit factors. For example, our data show alcohol-associated BrCa risk in women $\geqslant$55 years old. These older women are the ones more likely to obtain probable benefit for athero-thrombotic disease from light-moderate alcohol intake.[31] Advice is best handled by individual health practitioners dealing with individual clients.

5. Conclusions

This analysis confirms the association of alcohol drinking and BrCa, with no evident difference in risk for the beverage types. The data suggest a risk threshold, with no increased BrCa risk among women consuming less than one drink per day. There was a concentration of an increased alcohol-related BrCa risk in women that were ER positive, indicating a probable hormone-mediated mechanism.

Conflict of interest statement

None declared.

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