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ORIGINAL PAPER

Alcohol Consumption and Risk of Breast Cancer by Tumor Receptor Expression

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Abstract In epidemiologic studies, alcohol consumption appears more strongly associated with risk of estrogen receptor (ER)-positive than ER-negative breast cancer. However, this association has not been assessed by other potentially relevant tumor markers, such as androgen receptor (AR) or insulin receptor (IR). In the prospective Nurses' Health Study cohort, we evaluated alcohol consumption and breast cancer risk by individual tumor marker expression (i.e., ER, progesterone receptor [PR], AR, and IR) while controlling for other markers and also assessed the joint effect of these receptors. During 26 years follow-up of 106,037 women, 2552 invasive breast cancers contributed to the analysis. When all four markers were considered simultaneously, no significant heterogeneity of the alcohol and breast cancer association was observed by any of the markers. However, each increment in one drink per day was associated with 10 % (95 % confidence interval [CI]=4 %, 15 %) and 9 % (95 % CI=4 %, 15 %) increased risk of AR-positive and ER-positive breast cancer, respectively, while no increased risk was observed among AR-negative or ER-negative tumors. The association was independent of PR and IR expression. Assessment of the joint expression of hormone receptors revealed a significantly increased risk among AR+/ER+/PR+ (hazard ratio [HR] per drink/day= 1.11, 95 % CI=1.06, 1.17) but not in other subgroups (e.g., AR−/ER−/PR−: HR=0.99; 95 % CI=0.88, 1.12). Our data suggest that the alcohol and breast cancer association may be more pronounced among ER-positive and/or AR-positive breast tumors. However, our data do not support an important role of IR in the association.

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Introduction

Alcohol consumption, even low to moderate intake, is a consistent risk factor for breast cancer in epidemiologic studies, with approximately 10–20 % increase in risk for three to six drinks per week compared to nondrinkers [1–3]. In prospective cohort studies, similar or stronger positive associations compared to all breast cancer cases combined have been reported for tumors expressing estrogen receptor (ER) or both ER and progesterone receptor (PR) [2, 4–6]. Moreover, alcohol consumption increases circulating estrogen levels [7–11].

However, the alcohol and breast cancer association has never been evaluated according to other potential biomarkers in breast cancer, such as the androgen receptor (AR) or the insulin receptor (IR). AR has important physiological effects in normal breast development, is expressed in >70 % of malignant breast tissue [12, 13], and has been reported as a favorable prognostic factor for breast cancer survival [14].

Although studies addressing the role of AR in breast cancer etiology are limited, pre-diagnostic circulating levels of androgens are consistently positively associated with breast cancer risk [15–17]. Also, alcohol intake has been positively correlated with circulating androgen levels, particularly dehydroepiandrosterone sulfate, in controlled intervention trials and cross-sectional studies [7–11, 18]. IR has also been hypothesized to be involved in breast cancer as it is overexpressed in the majority of breast cancer [19, 20], with increasing supporting data from experimental and clinical studies [21]. Interestingly, while alcohol consumption is positively correlated with circulating androgens, it is associated with improved insulin sensitivity and decreased circulating insulin in both observational and controlled diet studies [22–24]. Furthermore, recent prospective studies of circulating pre-diagnostic insulin or c-peptide and breast cancer risk suggest a positive association [25, 26], although no overall significant association was found in a meta-analysis of earlier prospective studies [27].

Previous studies suggest that breast cancer risk profiles vary according to tumor marker expression [28, 29]. Therefore, we proposed to evaluate alcohol consumption and breast cancer risk by several hormone receptors, individually and simultaneously, in the Nurses' Health Study (NHS) cohort.

Material and Methods

Study Population

Details of the study design of the NHS and the study population have been reported elsewhere [2, 30]. Briefly, the NHS was established in 1976 when 121,701 US female registered nurses, aged 30–55 years, completed an initial mailed questionnaire. The cohort has been followed biennially by mailed questionnaire to update information on exposure status and ascertain newly diagnosed diseases. The analytic period started in 1980 when alcohol consumption was first assessed. A total of 106,037 entered the analysis after exclusion of participants who developed cancer or died before 1980 (N=5652) and those with missing alcohol data at baseline and during follow-up (N=10,012). The study was approved by the Committee on the Use of Human Subjects in Research at the Brigham and Women's Hospital. Informed consent was obtained from all women participating in the study.

Assessment of Alcohol Consumption and Covariates

The assessment of alcohol consumption has been described in detail elsewhere [2]. In brief, information was first collected in 1980 when participants reported their average frequency of intake for each alcoholic beverage (i.e., beer, wine, and liquor) during the previous 12 months through a semiquantitative food frequency questionnaire, and updated in 1984, 1986, 1990, 1994, 1998, and 2002. Alcohol intake (grams per day) was calculated as the sum of the daily number of drinks multiplied by the average alcohol content of each type of alcoholic beverage (12.8 g of alcohol per beer, 11.0 g per glass of wine, and 14.0 g per serving of liquor). We then calculated cumulative average intake by averaging alcohol consumption over time using all available information beginning in 1980; we considered this the primary exposure variable in our analysis because it was the exposure definition mostly strongly associated with breast cancer risk in our prior analysis [2]. Alcohol intake ascertained from a self-report food frequency questionnaire was found to be very similar with that calculated from detailed diet records in a sample of 173 women in the NHS cohort (Spearman r=0.90) [31].

Covariates data, such as age at menarche, age at first birth, parity, family history of breast cancer, diagnosis of benign breast disease, weight, smoking, menopausal status, and menopausal hormone therapy (MHT) use, was obtained from the NHS questionnaire at baseline or the subsequent biennial questionnaires.

Ascertainment of Breast Cancer Cases

Breast cancer cases were identified through self-report on biennial questionnaires. All women reporting incident diagnoses of breast cancer were asked for permission to review their medical records; for cases for which pathology reports were obtained, cases were confirmed by medical record review (99 %). Deaths were ascertained through reporting by next of kin or postal authorities or searching the National Death Index, and approximately 98 % of deaths in the NHS have been identified by these methods [32, 33].

Tissue Microarrays and Immunohistochemical Analysis

Details of breast cancer tissue block collection and tissue microarray (TMA) construction have been described previously [34]. Briefly, we collected archived formalin-fixed paraffin-embedded breast cancer blocks from participants with incident breast cancers diagnosed 1980–2006. Of 7964 invasive tumors that were eligible for block collection, 4054 (51 %) were finally included in TMAs; of blocks not included in TMAs, the majority had been destroyed by the hospital, or there was insufficient tumor in the block for TMA construction. TMAs were constructed in the Dana Farber Harvard Cancer Center Tissue Microarray Core Facility, Boston, Massachusetts. Three cores, 0.6 mm in diameter, were obtained from each breast cancer sample and inserted into the recipient TMA blocks.

We performed immunohistochemical (IHC) assessments for AR, ER, PR, and IR on 5 μm paraffin sections cut from

the TMA blocks [13, 34] (Supplementary Table 1) and completed the assessment for 3598 cases. Cases included in TMAs contributing to this analysis were very similar to all eligible invasive cases in terms of demographics, breast cancer risk factors, and tumor characteristics (Supplementary Table 2). For AR, ER, and PR, TMA slides were read by an independent pathologist; tumor cells that showed any nuclear staining of AR, ER, or PR (≥1 % of nuclei staining positive) were considered AR-, ER-, or PR-positive, respectively. AR expression was determined by TMA slides exclusively, while ER and PR were determined primarily from TMA slides and secondarily from pathology reports if information was missing from TMA slides. IR expression (cytoplasmic and membranous) was quantified using Definiens image analysis software (Tissue Studio, Definiens AG, Munich, Germany). We calculated an IR H-score as a weighted sum of the intensity of IHC cytoplasmic and membranous expression as follows: H-score=% of positively stained cells at weak intensity category *X* 1+% of positively stained cells at median intensity category *X* 2+% of positively stained cells at high intensity category *X* 3 [35]. In a subset of the cases (*N*=124), we assessed the correlation of IR expression between manual reading by expert pathologist and the image analysis, and observed a sensitivity and specificity of 83 and 69 %, respectively, for the image analysis if considering the manual reading as the gold standard. The median of the H-score was chosen as the cutoff to determine IR positivity: positive if H-score>the median value. Because there has not been an established standard cutoff point for determining IR expression status, we performed sensitivity analyses using different cutoff points (i.e., >33 vs. ≤33 %, or >75 vs. ≤75 %) for the IR H-score. Five hundred forty tumors with missing information on any of the four tumor markers and an additional small subset of ER−/PR+ tumors (*n*=47) were excluded from the analysis.

Statistical Analysis

For this analysis, follow-up time accrued from 1980 when alcohol consumption was first assessed until the diagnosis of any type of cancers, death, or June 2006. Only invasive breast cancer cases were included in the analysis; noninvasive cases or invasive cases not included in TMA were censored. A constrained Cox competing-risk survival model [36] which allows for assessment of heterogeneity of alcohol and breast cancer association according to specific tumor marker while accounting for other markers was used to estimate hazard ratio (HR) and 95 % confidence interval (CI). We used this model because stratification of data according to multiple marker subtypes becomes impractical given that a small number of cases in some strata and some of the markers are highly correlated (e.g., ER and AR). Wald tests were used to assess if the association differed by tumor marker expression (i.e., positive vs. negative). Covariates included in the model were common breast cancer risk factors and possible confounders (details in footnotes of Table 3). We first evaluated the alcohol and breast cancer association by considering each tumor marker separately and then assessed the association for each marker while accounting for other tumor markers. For instance, when evaluating the association according to AR expression, we first fit the model according to AR subtypes without considering other tumor markers; we then estimated adjusted hazard ratios taking into account other tumor markers (i.e., ER, PR, and IR), controlling for heterogeneity of the alcohol and breast cancer association according to these tumor markers. Tests for trend were performed by modeling the median values of alcohol intake categories as a continuous variable in the multivariable models.

We also assessed the joint expression of AR, ER, and PR by stratifying data according to specific marker subtypes in standard Cox proportional hazards model [37]. IR was not included in this analysis because no evidence of significant heterogeneity of the alcohol and breast cancer association according to IR subtypes was found, and in a preliminary analysis, similarly, no heterogeneity was observed by further including IR with AR, ER, and PR classifications, and case numbers were small in many of these 4-receptor subtype categories. Likelihood ratio tests were used to assess global heterogeneity and pairwise difference between subgroups. We further classified subtypes according to the number of positive tumor markers, defined as an ordinal number (i.e., 0, 1, 2, 3) and performed a trend test to assess if the alcohol and breast cancer risk increases as the number of positive tumor markers increase. All analyses were performed using SAS version 9.3 with a two-sided significance *P* value of <0.05.

Results

Table 1 presents the characteristics of the study population according to cumulative average alcohol consumption in 1992, the midpoint of the follow-up time. Most characteristics were approximately evenly distributed across the groups except that increasing levels of alcohol consumption were correlated with lower current BMI and women who consumed higher alcohol were more likely to be current smokers. Among postmenopausal women, nondrinkers were less likely to be MHT users compared to alcohol consumers, although among alcohol drinkers, there was no clear linear trend for MHT use across increasing levels of alcohol intake.

A total of 1975 tumors (77 %) were AR+, 2054 (80 %) were ER+, 1754 (69 %) were PR+, and 1277 (50 %) were IR+, respectively (Table 2). AR expression was highly correlated with ER and PR expression: Compared to ER− tumors, ER+ tumors were approximately 8.7 times (95 % CI=7.0, 10.8) more likely to be AR+; compared to PR- tumors, PR+ tumors were also more likely to be AR+ (OR=4.9, 95 % CI=

Table 1 Characteristics of study population in 1992

	Cumulative average daily alcohol intake, g/day					
	0	>0–<5	5–<10	10–<20	20–<30	≥30
All women, no.	21310	37897	12076	11039	3961	3227
Age, year	59.1(7.2)	58.1(7.2)	58.3(7.1)	58.9(7.0)	59.3(6.9)	59.92(6.7)
Age at menarche, year	12.4(1.8)	12.4(1.8)	12.5(1.8)	12.5(1.8)	12.5(1.7)	12.49(1.8)
Nulliparous, %	5	5	6	7	7	8
Parity[a]	2.8(0.7)	2.8(0.7)	2.8(0.7)	2.8(0.7)	2.8(0.7)	2.8(0.7)
Age at first birth, year	25.2(3.4)	25.1(3.3)	25.1(3.3)	25.1(3.3)	25.0(3.2)	25.1(3.3)
BMI at 18 yrs, kg/m^2	21.7(3.3)	21.5(3.0)	21.1(2.6)	21.1(2.7)	21.0(2.5)	21.13(2.8)
BMI, kg/m^2	27.3(5.7)	26.6(5.2)	25.4(4.4)	24.9(4.1)	24.8(4.0)	24.84(4.2)
Age at menopause[b], year	48.9(4.7)	49.0(4.7)	49.1(4.8)	49.1(4.4)	49.1(4.3)	49.04(4.0)
Premenopausal, %	15	16	16	15	15	14
Current MHT use, %	33	38	41	41	42	35
Current smoker, %	11	14	15	20	22	34
Family history of breast cancer in a first degree relative, %	11	12	12	13	12	12
History of benign breast disease, %	41	43	45	44	44	40

All variables except age are age standardized

[a] Among parous women

[b] Among women with natural menopause or bilateral oophorectomy

4.1, 6.0). However, AR expression was moderately correlated with IR expression: IR+ tumors were about 1.8 (95 % CI=1.4, 2.1) times more likely to be AR+, compared to IR− tumors.

Because only cases who had information on all four tumor markers contributed to the analysis, we first evaluated alcohol consumption and risk of breast cancer among these cases to compare results with those from a larger analysis of all cases diagnosed 1980~2008 [2] and found that the association was similar in our study population as in the larger data set. We found that consumption of at least 30 g alcohol per day (vs. no alcohol consumption) was associated with an increased risk of breast cancer (RR=1.41, 95 % CI=1.16, 1.72), which is consistent and similar to results in our earlier report (RR=1.51, 95 % CI=1.35, 1.70), although no significantly increased risk was observed among low to moderate alcohol consumers in the current study population (data not shown). A similar dose–response relationship also was observed (RR per 11 g/day:1.09; 95 % CI=1.04, 1.13) compared to that in the earlier study (RR per 10 g/day:1.10; 95 % CI=1.07, 1.12).

Table 2 Joint distribution of AR, ER, PR, and IR expression among invasive breast cancer cases (*N*=2552), Nurses' Health Study 1980–2006

AR	ER	PR	IR	No. of Cases	%
+	+	+	+	854	33.5
+	+	+	−	667	26.1
−	−	−	−	181	7.1
−	+	+	−	135	5.3
+	−	−	−	133	5.2
+	+	−	−	125	4.9
+	+	−	+	122	4.8
−	−	−	+	110	4.3
−	+	+	+	98	3.8
+	−	−	+	74	2.9
−	+	−	−	34	1.3
−	+	−	+	19	0.7

When considering each tumor marker separately, we did not find any significant heterogeneity of the alcohol and breast cancer association by hormone receptor status ($P_{heterogeneity}$ range 0.06–0.99; Table 3). However, increasing alcohol consumption appeared similarly positively associated with risk of AR+, ER+, or PR+ breast cancer but not AR−, ER−, or PR− breast cancer. For example, each increment of 11 g alcohol (approximately one drink) per day was associated with a 10 % increased risk (HR=1.10, 95 % CI=1.05, 1.16) of AR+ breast cancer, while there was no apparent dose–response relationship among AR− breast cancer (HR=1.02, 95 % CI=0.93, 1.13). Comparable results were observed for ER and PR. Similarly, an increased risk, of approximately 50 %, was seen among women who consumed at least 30 g of alcohol daily (vs. nondrinkers) for AR+, ER+, and PR+ breast cancer respectively but not for AR−, ER−, or PR− breast cancer. The significantly increased risk was observed only among the highest alcohol category (i.e., ≥30 g/day) but not in low to moderate alcohol categories (e.g., 20–<30 g/day) in AR+, ER+, and PR+ tumors, respectively, although a statistically

Table 3 Alcohol consumption and breast cancer risk according to AR, ER, PR, and IR subtypes, Nurses' Health Study 1980–2006

	Cumulative average daily intake (g/day)							
	0	>0–<5	5–<10	10–<20	20–<30	≥30	*P*-trend	Per 11 g/day
AR-positive								
Cases, no.	442	792	266	285	86	104		
HR (95 % CI)[a]	1.00 *Ref*	1.05 (0.93, 1.18)	1.09 (0.93, 1.27)	1.17 (1.00, 1.36)	1.05 (0.83, 1.33)	1.50 (1.20, 1.86)	0.001	1.10 (1.05, 1.16)
AR-negative								
Cases, no.	155	236	70	70	20	26		
HR (95 % CI)[a]	1.00 *Ref*	0.89 (0.73, 1.10)	0.84 (0.63, 1.12)	0.87 (0.65, 1.17)	0.75 (0.47, 1.21)	1.19 (0.78, 1.82)	0.94	1.02 (0.93, 1.13)
P-het[b] 0.16 and *P*-het[c] 0.17								
ER-positive								
Cases, no.	470	817	272	298	86	111		
HR (95 % CI)[a]	1.00 *Ref*	1.01 (0.90, 1.13)	1.04 (0.90, 1.21)	1.15 (0.99, 1.33)	0.99 (0.79, 1.25)	1.53 (1.24, 1.89)	0.0004	1.10 (1.05, 1.16)
ER-negative								
Cases, no.	127	211	64	57	20	19		
HR (95 % CI)[a]	1.00 *Ref*	1.01 (0.81, 1.26)	0.97 (0.71, 1.32)	0.87 (0.63, 1.20)	0.93 (0.57, 1.49)	1.01 (0.62, 1.65)	0.62	1.01 (0.91, 1.13)
P-het[b] 0.06 and *P*-het[c] 0.15								
PR-positive								
Cases, no.	399	695	239	254	74	93		
HR (95 % CI)[a]	1.00 *Ref*	1.00 (0.89, 1.14)	1.08 (0.92, 1.27)	1.16 (0.99, 1.37)	1.02 (0.79, 1.31)	1.54 (1.22, 1.94)	0.0005	1.11 (1.05, 1.16)
PR-negative								
Cases, no.	198	333	97	101	32	37		
HR (95 % CI)[a]	1.00 *Ref*	1.02 (0.85, 1.22)	0.92 (0.72, 1.18)	0.95 (0.74, 1.22)	0.90 (0.62, 1.32)	1.19 (0.83, 1.70)	0.86	1.04 (0.96, 1.13)
P-het[b] 0.08 and *P*-het[c] 0.20								
IR-positive								
Cases, no.	301	520	163	178	51	64		
HR (95 % CI)[a]	1.00 *Ref*	1.00 (0.86, 1.15)	0.98 (0.81, 1.20)	1.10 (0.91, 1.33)	0.94 (0.69, 1.27)	1.43 (1.09, 1.89)	0.04	1.08 (1.01, 1.15)
IR-negative								
Cases, no.	296	508	173	177	55	66		
HR (95 % CI)[a]	1.00 *Ref*	1.02 (0.88, 1.18)	1.07 (0.88, 1.30)	1.09 (0.90, 1.32)	1.02 (0.76, 1.36)	1.41 (1.07, 1.85)	0.03	1.10 (1.03, 1.16)
P-het[b] 0.99 and *P*-het[c] 0.70								

[a] Adjusted for first-degree family history of breast cancer, history of benign breast disease, age (continuous), age at menarche (<12, 12, 13, 13+, missing), age at first birth and no. of children (nulliparous, one to two children and <25 years, one to two children and 25–29 years, one to two children and ≥30 years, three to four children and <25 years, three to four children and 25–29 years, three to four children and ≥30 years, >four children and <25 years, >four children and ≥25 years, missing category), BMI (<23, 23–<25, 25–<27.5, 27.5–<30, 30–<35, 35+, missing, kg/m^2), smoking (never, former, current, missing), menopausal hormone therapy use (never, past user, current <5 years, current >5 years, premenopausal, missing), age at menopause (continuous), and missing indicator for age at menopause

[b] *P* value for heterogeneity test of marker expression positive vs. negative when alcohol evaluated as a categorical variable

[c] *P* value for heterogeneity test of marker expression positive vs. negative when alcohol evaluated continuously as 11 g/day

significant linear trend was observed. In contrast, hazard ratios were very similar comparing IR+ with IR− breast tumors ($P_{\text{heterogeneity}}$=0.99 and 0.70, when alcohol assessed as categorical or per 11 g/day, respectively). Each additional drink daily was significantly associated with about 8 % (95 % CI= 1 %, 15 %) and 10 % (95 % CI=3 %, 16 %) increased risk of IR+ and IR− breast cancer, respectively. Sensitivity analyses using different cutoff points for the IR H-score found that results were essentially unchanged when IR positivity was defined as either >33 % (vs. ≤33 %) or >75 % (vs. ≤75 %) (data not shown).

When considering the four tumor makers simultaneously, there again was no significant heterogeneity for any of the four markers, although some suggestive differences were seen (Table 4). Compared to results when each tumor marker was considered separately (Table 3), hazard ratios from the adjusted models remained similar among AR+, ER+, or PR+ breast cancer. However, associations for AR−, ER−, or PR− tumors became more similar to the hormone receptor positive associations, although these changes varied somewhat by receptor. Alcohol associations for AR− became more similar to AR+, particularly in the categorical model. Compared to women

Table 4 Alcohol consumption and breast cancer risk according to AR, ER, PR, and IR subtypes after accounting for other markers, Nurses' Health Study 1980–2006

	Cumulative average daily intake (g/day)							
	0	>0–<5	5–<10	10–<20	20–<30	≥30	*P*-trend	Per 11 g/day
AR-positive								
Cases, no.	442	792	266	285	86	104		
HR (95 % CI)[a]	1.00 *Ref*	1.06 (0.94, 1.19)	1.10 (0.94, 1.29)	1.15 (0.98, 1.35)	1.07 (0.84, 1.35)	1.44 (1.15, 1.81)	0.004	1.10 (1.04, 1.15)
AR-negative								
Cases, no.	155	236	70	70	20	26		
HR (95 % CI)[a]	1.00 *Ref*	0.87 (0.69, 1.09)	0.83 (0.61, 1.13)	0.91 (0.67, 1.25)	0.73 (0.44, 1.21)	1.31 (0.84, 2.05)	0.56	1.04 (0.94, 1.15)
P-het[b] 0.49 and *P*-het[c] 0.37								
ER-positive								
Cases, no.	470	817	272	298	86	111		
HR (95 % CI)[a]	1.00 *Ref*	1.00 (0.88, 1.13)	0.98 (0.82, 1.17)	1.12 (0.94, 1.32)	0.94 (0.72, 1.22)	1.51 (1.19, 1.90)	0.005	1.09 (1.04, 1.15)
ER-negative								
Cases, no.	127	211	64	57	20	19		
HR (95 % CI)[a]	1.00 *Ref*	1.05 (0.76, 1.46)	1.25 (0.80, 1.97)	0.99 (0.63, 1.55)	1.15 (0.58, 2.28)	1.08 (0.56, 2.09)	0.91	1.04 (0.91, 1.20)
P-het[b] 0.42 and *P*-het[c] 0.58								
PR-positive								
Cases, no.	399	695	239	254	74	93		
HR (95 % CI)[a]	1.00 *Ref*	1.00 (0.86, 1.15)	1.11 (0.91, 1.35)	1.11 (0.92, 1.35)	1.02 (0.76,1.38)	1.43 (1.09, 1.88)	0.02	1.09 (1.03, 1.16)
PR-negative								
Cases, no.	198	333	97	101	32	37		
HR (95 % CI)[a]	1.00 *Ref*	1.04 (0.81, 1.32)	0.87 (0.62, 1.22)	1.04 (0.76, 1.43)	0.88 (0.53, 1.46)	1.36 (0.88, 2.11)	0.45	1.07 (0.97, 1.18)
P-het[b] 0.61 and *P*-het[c] 0.73								
IR-positive								
Cases, no.	301	520	163	178	51	64		
HR (95 % CI)[a]	1.00 *Ref*	0.99 (0.86, 1.15)	0.97 (0.80, 1.18)	1.07 (0.88, 1.30)	0.92 (0.68, 1.25)	1.39 (1.05, 1.84)	0.08	1.07 (1.00, 1.14)
IR-negative								
Cases, no.	296	508	173	177	55	66		
HR (95 % CI)[a]	1.00 *Ref*	1.02 (0.88, 1.19)	1.09 (0.90, 1.32)	1.11 (0.91, 1.34)	1.03 (0.77, 1.39)	1.43 (1.09, 1.88)	0.02	1.10 (1.04, 1.16)
P-het[b] 0.74 and *P*-het[c] 0.52								

[a] Adjusted for the same covariates as in footnote a in Table 3 and further adjusted for other tumor markers

[b] *P* value for heterogeneity test of marker expression positive vs. negative when alcohol evaluated as a categorical variable

[c] *P* value for heterogeneity test of marker expression positive vs. negative when alcohol evaluated continuously as 11 g/day

who never consumed alcohol, women who consumed ≥30 g/day alcohol had a 44 % increased risk of AR+ breast cancer (95 % CI=1.15, 1.81) and a nonsignificant 31 % increased risk for AR− breast cancer (95 % CI=0.84, 2.05). For ER, compared to Table 3 findings, hazard ratios after accounting for the other markers were largely unchanged. For example, consumers of ≥30 g/day of alcohol (compared to nonusers) had a 51 % higher risk of ER+ tumors (95 % CI=1.19, 1.90) but an 8 % increased risk of ER− tumors (95 % CI=0.56, 2.09). Similar to results in Table 3, among AR+ or ER+ breast tumors, a significantly increased risk was seen only in the ≥30 g/day alcohol category, although a significant dose–response relationship also was observed. For IR and PR, the hazard ratios associated with alcohol intake among hormone receptor positive tumors looked very similar to those for hormone receptor negative tumors $P_{\text{heterogeneity}}$ (range 0.52~0.74).

The assessment of joint expression of AR, ER, and PR showed that increased risk was observed among tumors expressing all three markers (HR for per drink daily 1.11; 95 % CI=1.06, 1.17) but not among the AR−/ER−/PR− subgroup (HR=0.99; 95 % CI=0.88, 1.12) (Table 5). Despite no significant overall heterogeneity across all subgroups ($P_{\text{heterogeneity}}$= 0.22), the pair-wise comparison between AR+/ER+/PR+ and AR−/ER−/PR− was significant ($P_{\text{heterogeneity}}$=0.03). When classifying subtypes according to number of positive tumor

Table 5 Alcohol consumption and breast cancer risk according to specific subtypes of AR, ER, and PR, Nurses' Health Study 1980–2006

	No. of cases	HR[a]	95 % CI
AR+/ER+/PR+	1521	1.11	1.06, 1.17
AR+/ER+/PR−	247	1.09	0.97, 1.23
AR−/ER+/PR+	233	1.06	0.94, 1.19
AR+/ER−/PR−	207	1.04	0.93, 1.18
AR−/ER+/PR−	53	1.04	0.89, 1.21
AR−/ER−/PR−	291	0.99	0.88, 1.12

[a] Hazard ratios for each increment of per alcohol drink per day, adjusting for the same covariates as in footnote a in Table 3

markers, we observed that increasing number of positive markers was associated with increased hazard ratios (P_{trend}= 0.03). For instance, no association was observed among tumors negative for AR, ER, and PR (HR per drink daily 0.96; 95 % CI=0.83, 1.10), while modestly increased risk was found among tumors expressing at least two (HR=1.11, 95 % CI=1.01, 1.22) or three (HR=1.12, 95 % CI=1.06, 1.18) of the hormone markers.

Discussion

We evaluated adult alcohol consumption and risk of breast cancer according to tumor hormone receptors in a large prospective study over a 26-year period. After taking into account possible heterogeneity of the alcohol and breast cancer association by other tumor markers, increasing alcohol consumption was positively associated with risk of ER+ or AR+ breast cancer, but not ER− or AR− breast cancer, although this difference was not statistically significant. However, the alcohol and breast cancer association appeared independent of IR and PR expression. Finally, when assessing the joint expression of tumor hormone receptors, the association was more pronounced among strong hormone positive tumors (i.e., AR+/ER+/PR+).

To our knowledge, our study provides the first evaluation of the association between alcohol and breast cancer risk by tumor AR and IR expression. However, both receptors have been evaluated in relation to breast cancer prognosis. AR has been consistently associated with better prognosis [14], primarily among ER positive tumors [14], while data for IR are more limited and inconsistent [38, 39]. Although the alcohol and breast cancer association did not significantly vary by tumor IR expression in our study, insulin and IR have gained more interest, as increasing experimental and preclinical data have supported the possible role of IR in breast cancer etiology [21]. Interestingly, as we mentioned earlier, alcohol consumption can improve insulin sensitivity and is inversely correlated with circulating insulin levels, which is contrary to the positive correlation seen between alcohol intake and circulating steroids hormones, such as estrogens and androgens. Further epidemiologic studies evaluating the potential influence of these two receptors in mediating lifestyle and breast cancer associations would be useful. Furthermore, we assessed IR expression, for the first time, using computer-assisted digital image analysis (i.e., Definiens) instead of manual reading by a pathologist. While the digital analysis saves substantial time and cost, no study has evaluated the consistency between the two methods, particularly for IR. We observed a sensitivity and specificity of 83 and 69 %, respectively, for the image analysis if considering the manual reading as the gold standard in a subset of the cases. However, this requires confirmation in future studies that apply the digital analysis.

Whether the association of alcohol intake and breast cancer risk varies by ER and PR status of the tumor has been assessed in a number of studies. A meta-analysis of four prospective cohort and 16 case–control studies reported that per 10 g/day alcohol was associated with 12 % (95 % CI=8 %, 15 %) increased risk of all ER+ breast cancer but not ER−/PR− breast cancer (HR=1.04, 95 % CI=0.98, 1.09), with significant heterogeneity between all ER+ and ER−/PR− [4]. In two subsequent cohort studies, for each increment of one drink/day, a slightly but significantly increased (5–8 %) risk was observed for ER+/PR+ breast cancer, while neither study found an association for ER−/PR− breast cancer [5, 6]. Our earlier study of 7690 cases diagnosed 1980–2008 in the NHS that also observed positive associations among ER+/PR+ and ER+/PR− breast cancer but not among ER−/PR− tumors, although this difference was not statistically significant [2]. However, two recent prospective studies found that the alcohol and breast cancer association appeared independent of ER and PR status [3, 40]. Consistent with most of the previous studies, we found that the alcohol and breast cancer association varied suggestively by ER status when ER was considered individually or simultaneously with other tumor markers, although the differences were not statistically significant.

Although the alcohol and breast cancer association did not vary significantly by AR expression status individually, when evaluating joint expression of AR, ER, and PR, a significantly increased risk was observed in tumors expressing all three markers (i.e., AR+/ER+/PR+), while no association was seen in the AR−/ER−/PR− subgroup, with significant difference between these two categories. Thus, it appears that androgen signaling, in addition to estrogen signaling, may be involved in the alcohol and breast cancer association and may biologically interact with estrogens. Supporting data are the observations that no significant heterogeneity was found for any of the three hormone receptors when they were mutually adjusted, while the joint estrogen and androgen signaling showed significant increased risk (vs. AR−/ER−/PR− tumors). Taken together, our data suggest that the alcohol and breast cancer

association may be more pronounced among sex steroid hormone-sensitive tumor subgroup(s) although additional large studies are needed to confirm this finding.

A major strength of this study was the assessment of alcohol consumption and risk of breast cancer by several breast tumor markers, of which AR and IR were evaluated for the first time. Other strengths included prospective measurement of alcohol consumption with updated exposure information, a large number of invasive breast cancer cases, and use of a constrained competing-risk survival model which allows the assessment of heterogeneity of the association while taking into account the other tumor markers. Our study also has several limitations. The cases contributing to this analysis was a subset of all eligible cases in the cohort; however, cases from whom tumor marker information were not available were not significantly different from cases included in this analysis in terms of characteristics and accepted breast cancer risk factors (Supplementary Table 2). Another limitation is that since no standard method has been established for determining IR positivity, we chose to use the IR H-score and consider the median of the H-score as the cutoff point to determine IR positivity. However, sensitivity analysis showed that the association did not vary by different cutoff points of the H-score (e.g., 33 % or 75 %). Additionally, we observed only moderate sensitivity and specificity when comparing manual pathologist assessment vs. image analysis results for IR, suggesting some potential misclassification in our IR definition that could decrease our ability to detect different associations by IR status.

To summarize, we did not find that the alcohol and breast cancer association significantly varied according to each of the four tumor markers assessed (i.e., AR, ER, PR, and IR), after considering these tumor markers simultaneously. However, assessment of joint effect of androgen and estrogen signaling suggests a possible biological interaction between these two pathways. Our data also did not support an important role for IR and PR in the alcohol and breast cancer association. These findings highlight the importance of incorporating breast cancer subtypes in determining risk factor associations. Further studies are warranted to confirm these findings and may extend to other relevant markers in order to better understand the underlying mechanism of the effect of alcohol consumption on breast cancer risk.

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Conflict of Interest The authors declare that they have no conflict of interest.

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