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Alcohol Consumption and Breast Cancer Risk According to Hormone Receptor Status in Japanese Women: A Case-Control Study

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Alcohol consumption is a risk factor for breast cancer in Western countries, but few studies have evaluated the risk for Japanese women, who have a relatively low alcohol intake. This case-control study investigated the association of alcohol consumption with breast cancer risk according to estrogen-receptor and progesterone-receptor (ER/PgR) status in Japanese women. From female patients aged 30 years and over admitted to a single hospital in Japan between 1997 and 2011, 1,256 breast cancer cases (669 ER+/PgR+, 162 ER+/PgR−, 21 ER−/PgR+, 305 ER−/PgR−, and 99 missing) and 2,933 controls were selected. Alcohol-related measures were assessed using a self-administered questionnaire. Unconditional logistic regression analysis was performed. Alcohol-related measures were not associated with breast cancer risk among the women overall. Moreover, no association was observed between ever drinking and the risk of a concordant receptor subtype (ER+/PgR+ or ER−/PgR−). Conversely, ever drinking was inversely associated with the risk of discordant subtype (ER+/PgR−, odds ratio (OR) = 0.63, 95% confidence interval (CI): 0.41-0.95; ER−/PgR+, OR = 0.44, 95% CI: 0.14-1.42). For ER+/PgR−, an inverse association with the amount of alcohol consumed per day was observed (*P* for trend = 0.04), and this inverse association was limited to premenopausal women. Alcohol consumption may have differential effects on concordant and discordant receptor subtypes of breast cancer. In view of the low frequency of discordant subtype in Japanese women and their relatively low alcohol intake, our findings may provide a clue for elucidating the etiology of breast cancer rather than for preventing discordant subtype.

Keywords: alcohol; breast cancer; hormone receptor; Japanese; menopausal status
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Introduction

Breast cancer is one of the most common cancers worldwide, and numerous epidemiologic studies of breast cancer have been conducted in a large number of populations. Reproductive factors including early menarche and low parity and anthropometric factors including tallness, and postmenopausal obesity have been identified as risk factors for breast cancer (Kelsey et al. 1993; World Cancer Research Fund and American Institute for Cancer Research 2007).

Among lifestyle factors related to breast cancer risk, alcohol consumption has been considered important in Western countries (Longnecker 1994; Smith-Warner et al. 1998). Epidemiological studies conducted mainly in Western countries have shown that alcohol consumption is associated with an increased risk of breast cancer (Hamajima et al. 2002; Key et al. 2006), and it is now regarded as an established breast cancer risk factor (Baan et al. 2007). Among the Japanese population, however, a qualitative review of the existing evidence has indicated that the association between alcohol consumption and breast cancer risk remains inconclusive (Nagata et al. 2007). Some recent studies investigating the risk among Asian women have yielded conflicting result. Our previous cohort study including Japanese women found no associa-

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tion between alcohol consumption and breast cancer risk (Kawai et al. 2011). A meta-analysis of 4 case-control studies conducted in China found a significant inverse association between alcohol consumption and breast cancer risk (Li et al. 2011), and a population-based case-control study of Asian-American women concluded that alcohol consumption was a significant risk factor for Japanese, but not for Chinese- or Filippino-Americans (Wu et al. 2012). These inconsistent results may have been due to differences in alcohol-related items among countries and regions, such as the amount of alcohol and the types of alcoholic beverage consumed. Otherwise, the distribution of hormone receptor status in breast tumors varies between Caucasian and Asian populations (Nomura et al. 1977), which may explain the difference in overall association between alcohol consumption and breast cancer risk. Some previous studies have demonstrated variation in the magnitude of risk associated with alcohol-related items among the subtypes of breast cancer, alcohol consumption appearing to preferentially increase the risk of developing cancer with the expression of estrogen receptor and progesterone receptor (Enger et al. 1999; Rusiecki et al. 2005; Li et al. 2010; Falk et al. 2014). However, evidence for alcohol-related breast cancer risk in relation to hormone receptor status has been limited in both Japan and Western countries. In Japan, three studies have investigated alcohol-related breast cancer risk stratified by hormone receptor status (Yoo et al. 1997; Suzuki et al. 2010; Islam et al. 2013); however, information on hormone receptor status was incomplete among these three studies.

To clarify the association between alcohol consumption and breast cancer risk in relation to menopausal and hormone receptor status, we conducted a hospital-based case-control study. Data were obtained from women aged 30 years and over who were admitted to a single hospital in Miyagi Prefecture, Japan, between 1997 and 2011. Analyses were performed with reference to joint estrogen-receptor and progesterone-receptor (ER/PgR) status, i.e., ER+/PgR+, ER+/PgR−, ER−/PgR+, or ER−/PgR−. Japanese women are known to have background characteristics differing from Caucasian women, and most are low to moderate alcohol drinkers (World Health Organization 2014).

Methods

Data collection

In January 1997, we began a questionnaire survey in connection with the present study at the Miyagi Cancer Center Hospital (MCCH). The procedure used in this survey has already been described previously (Minami and Tateno 2003; Fujita et al. 2008; Kawai et al. 2012, 2013; Nishino et al. 2014). The purpose of the survey was explained on the cover page of the questionnaire. We considered the return of questionnaires signed by the patients to imply their consent to participate in the study.

The questionnaire covered demographic characteristics, personal and family histories of cancer and other diseases, current height and weight, general lifestyle factors including alcohol intake, dietary history, cigarette smoking, physical activity, occupation, menstrual and reproductive histories, and history of oral contraceptive (OC) use and other exogenous female hormone uses. Items related to the referral status and area of residence were also included. Dietary history and alcohol intake were assessed using a food frequency questionnaire (FFQ). Based on the average frequency of intake of 40 food items and 9 food groups during the year prior to the survey, the estimated intakes of nutrient and food per day were computed using the Japanese Standard Tables of Food Composition, fourth and fifth editions. The FFQ has been validated in a sub-sample of the Miyagi cohort, whose residential area was roughly the same as that of our study subjects (Ogawa et al. 2003). Between January 1997 and December 2011, the questionnaire was distributed to 26,984 first-admitted patients, of whom 24,062 responded.

Study subjects

Cases and controls were selected from among 24,062 respondents to the above questionnaire. The selection procedure has already been described elsewhere (Minami and Tateno 2003; Fujita et al. 2008; Kawai et al. 2012, 2013; Nishino et al. 2014).

Cases were identified as follows. A list of the respondents was linked with both the hospital-based cancer registry file and the disease registration database at the MCCH. Through this linkage, 24,062 respondents were classified into 2,219 with a past history of cancer, 7,707 males with cancer, 1,309 females with breast cancer, 4,779 females with other cancers, and 8,048 non-cancer respondents (4,170 males and 3,878 females). Among the 1,309 females with breast cancer, 1,302 aged 30 years and over were identified as the cases (Nishino et al. 2014). Information on the expression of ER and PgR in their breast tumors was extracted from the medical records.

Controls were selected from among the 3,878 female non-cancer respondents. After excluding respondents under 30 years of age, 3,587 female non-cancer respondents aged 30 years and over were selected as possible controls, from whom 502 patients with alcohol-related disease were excluded in order to avoid any bias due to over-representation of patients with diseases associated with the exposure variable (Schlesselman 1982; Rothman and Greenland 1998); these included 403 with digestive tract disease, 89 with benign nasopharyngeal tumors, and 10 with benign esophageal tumors. Finally, a total of 3,085 female non-cancer respondents were included as controls. The diagnoses among these controls were: benign tumor in 2,031 (65.8%), cardiovascular disease in 118 (3.8%), respiratory tract disease in 130 (4.2%), urologic-gynecologic disease in 176 (5.7%), endocrine or metabolic disease in 87 (2.8%), orthopedic disorder in 54 (1.8%), other benign disease in 207 (6.7%), and no abnormal findings in 282 (9.2%). The sites of benign tumors were the stomach in 156 subjects, the colorectum in 532, the lung in 21, the breast in 44, the gynecologic organs in 381, the urologic organs in 19, bone or connective tissue in 636 and other sites in 242. The final response rate for the questionnaire survey was 94.4% for the cases and 89.6% for the possible controls.

This study was approved by the ethical review boards of the Miyagi Cancer Center (Protocol Identification Number 23-18, September 16, 2011) and Tohoku University Graduate School of Medicine (Protocol Identification Number 2011-325, October 24, 2011).

Assessment of alcohol intake

For assessment of alcohol intake, the FFQ (Ogawa et al. 2003) asked initially if the subjects were never, past, or current drinkers.

Past or current drinkers were asked to state age at the start of drinking, the frequency of drinking, and the types of alcohol beverages consumed [Japanese *sake*, Japanese spirits (*shochu*), beer, whisky, wine and others]. For each type of alcohol beverage consumed, they were also asked to state the volume drunk after conversion into the Japanese *sake* equivalent by reference to a conversion table. One unit (180 ml) of Japanese *sake* contains 22.8 g of ethanol (alcohol). The amount of alcohol consumed per day was calculated as: (total amount of alcohol consumed per occasion (g)) × (frequency of drinking per week)/7. In the validation study of the FFQ, the Spearman correlation coefficient between the amount of alcohol consumed per day estimated from the FFQ and from diet records was 0.60 (Ogawa et al. 2003), indicating that alcohol intake was reasonably estimated by the FFQ.

Exposure variables related to alcohol drinking (alcohol-related measures) included history of alcohol drinking (never-, past-, current-drinker), age at the start of drinking, frequency of drinking, amount of alcohol consumed per occasion, and amount of alcohol consumed per day. In the present study, past drinkers who had quit alcohol drinking within one year before the present admission were regarded as current drinkers. Cut-off points for age at the start of drinking and the frequency of drinking were determined based on tertiles among the controls, respectively. Cut-off points for the amount of alcohol consumed were determined arbitrarily, with reference to previous studies including our previous study that had investigated the effects of low to moderate alcohol intake (Lin et al. 2005; Kawai et al. 2011; Li et al. 2011; Zhang and Holman 2011). In additional analysis, quartile points among ever drinkers were also employed as cut-off points for the amount of alcohol consumed per day.

Subjects for whom data on history of alcohol drinking were missing [n = 46 (3.5%) for cases and n = 152 (4.9%) for controls] were excluded from the subsequent analysis, leaving 1,256 cases and 2,933 controls.

Statistical analysis

We used unconditional logistic regression analysis to estimate breast cancer risk associated with alcohol consumption. Study subjects were categorized using the cut-off points for each exposure and odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for each category.

In the analysis, the following variables were considered to be potential confounding factors: age, year of recruitment, referral status (from screening, other), area of residence (Southern Miyagi prefecture, others), pack-years of smoking, occupation (house wife, administrative work, industrial work, agriculture, other), age at menarche, age at menopause, menopausal status (premenopausal, postmenopausal), parity number, age at first birth, family history of breast cancer in first-degree relatives (yes, no), physical activity (time spent exercising), body mass index (BMI), history of use of exogenous female hormones or OCs (ever, never), and nutrient intake including energy and energy-adjusted folate intake. Missing values were treated as an additional variable category.

First, we estimated the overall association between alcohol consumption and breast cancer risk. Second, separate analyses were conducted after dividing the subjects into those who were premenopausal and those who were postmenopausal. Third, case subjects were stratified according to joint hormone receptor status (ER+/PgR+, ER+/PgR−, ER−/PgR+, or ER−/PgR−) and receptor-specific risks were evaluated using polytomous unconditional logistic regression analysis. Fourth, the receptor-specific risk was re-evaluated based on stratification according to some selected potential factors, such as menopausal status, BMI (high or low), intake of folate (high or low intake per day) and exogenous female hormone use (ever, never). These potential factors may have modifiable effects on exposure variables.

Dose-response relationships were tested by treating each exposure category as a continuous variable. If necessary, we conducted Wald tests for heterogeneity of breast cancer risk across joint hormone receptor status. Values were regarded as significant if the two-sided P values were < 0.05. All analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC).

Results

Table 1 shows the distributions of background characteristics and known or possible risk factors for cases and for controls. Although some differences in the distributions were observed between cases and controls, one of the background characteristics, i.e., referral status (from screening, other) among total cases was relatively similar to that among controls (P = 0.19). Among the case subjects (n = 1,256), ER/PgR status was known for 1,157 (92.1%). Cases with ER+/PgR− tumors tended to be older, and were more likely to be naturally menopausal, to have had a later age at menarche and menopause, and to be multiparous. With regard to pack-years of smoking, cases and controls showed almost the same distribution. Cases with ER+/PgR+ tended to be current drinkers.

Table 2 shows the ORs and 95% CIs for alcohol-related measures among the subjects overall and also according to menopausal status. In the risk evaluation for the amount of alcohol, we also calculated the ORs for a heavy intake of ≥ 50.0 g per occasion and ≥ 30.0 g per day respectively. No overall association between history of alcohol drinking (ever, never) and breast cancer risk was observed (OR = 0.96, 95% CI: 0.81-1.12). No such association was observed for either pre- or post-menopausal women. Overall analysis or analyses according to menopausal status revealed no association between the frequency of alcohol drinking and breast cancer risk. Among premenopausal women, an increased risk was observed for those who had started to drink at a later age, but this was not statistically significant. Regarding the amount of alcohol consumed per day, ORs in the categories for a larger amount exceeded one among premenopausal women (OR = 1.49 for 15.0 g/day ≤ and < 30.0 g/day; OR = 1.18 for ≥ 30.0 g/day), but these ORs did not reach statistical significance.

Table 3 shows the results in relation to joint hormone receptor status. The association between history of alcohol drinking (ever, never) and breast cancer risk was unity for the ER+/PgR+ and ER−/PgR− (concordant) types. Analyses of other alcohol-related measures revealed no association for these concordant subtypes. On the other hand, an inverse association with history of alcohol drinking was observed for either the ER+/PgR− or ER−/PgR+ (discordant) type. For ER+/PgR− cancer, the OR for ever-

Table 1. Characteristics of cases and controls by hormone receptor status.

	Cases						Controls	
	Total	Hormone receptor						P-value[d]
		ER+/PgR+	ER+/PgR−	ER−/PgR+	ER−/PgR−	Missing		
Number of subjects	1256	669	162	21	305	99	2933	
Age group (years old) (%)								
30-39	6.1	6.6	3.1	9.5	5.3	10.1	9.8	< 0.01
40-49	23.3	26.3	16.7	42.9	22.6	12.1	17.9	
50-59	29.5	28.6	29.0	23.8	30.8	33.3	21.7	
60-69	23.7	22.7	32.1	14.3	22.6	21.2	24.9	
70 ≤	17.4	15.8	19.1	9.5	18.7	23.3	25.7	
Mean ± SD (years old)	57.3 ± 12.2	56.5 ± 12.2	59.6 ± 11.1	52.9 ± 11.7	57.6 ± 12.2	58.8 ± 13.3	59.0 ± 13.9	< 0.01
Menopausal status (%)[a]								
Premenopause	34.9	41.4	21.6	42.8	30.8	22.2	30.1	< 0.01
Natural menopause	45.3	40.8	59.9	38.1	47.2	47.5	44.4	
Artificial menopause	14.3	13.3	14.8	4.8	15.1	0.0	20.2	
Unknown menopausal status	5.5	4.5	3.7	14.3	6.9	30.3	5.3	
Year of recruitment (%)								
1997-2003	36.0	29.6	37.6	52.4	42.6	52.5	53.2	< 0.01
2004-2011	64.0	70.4	62.4	47.6	57.4	47.5	46.8	
Referrel status (%)								
From screening	18.6	21.4	20.4	14.3	15.4	8.1	20.4	0.19
Other	81.4	78.6	79.6	85.7	84.6	91.9	79.6	
Area of residence (%)								
Southern Miyagi prefecture	83.3	83.4	85.8	85.7	82.6	79.8	89.0	< 0.01
Other area	16.7	16.6	14.2	14.3	17.4	20.2	11.0	
Occupation (%)								
House wife[b]	20.3	18.7	22.8	23.8	19.3	29.3	21.6	< 0.01
Administrative work	27.2	31.1	25.9	23.8	21.3	22.2	23.2	
Industrial work	34.8	33.9	37.7	28.6	40.0	21.2	30.0	
Agriculture	5.8	5.7	3.7	9.5	6.6	7.1	9.3	
Other	11.9	10.6	9.9	14.3	12.8	20.2	15.9	
BMI (kg/m^2, %)								
< 18.5	5.4	4.9	6.2	-	5.3	9.1	5.9	0.02
18.5 ≤ < 25.0	61.9	59.5	64.8	61.9	65.9	61.6	64.2	
25.0 ≤ < 30.0	25.5	27.0	24.1	38.1	22.9	22.2	25.3	
30.0 ≤	6.6	8.1	4.9	-	5.6	4.1	3.8	
Missing	0.6	0.5	-	-	0.3	3.0	0.8	
Time spent exercising (%)								
Almost no	50.5	50.4	49.4	47.6	51.8	49.5	47.7	0.25
1 ≤ hr per week	43.1	44.1	43.8	47.6	41.0	40.4	46.3	
Missing	6.4	5.5	6.8	4.8	7.2	10.1	6.0	
Age at menarche (%)								
≤ 12	30.7	34.1	20.3	33.3	30.5	25.2	23.5	< 0.01
13	22.4	22.9	21.0	23.8	22.3	21.2	20.4	
14	20.3	18.8	27.2	19.1	21.3	16.2	18.4	
15 ≤	22.3	20.5	27.2	19.1	22.0	28.3	30.6	
Missing	4.3	3.7	4.3	4.7	3.9	9.1	7.1	
Age at menopause among natural menopausal women (%)								
< 48	14.4	15.0	7.2	25.0	16.0	19.2	17.3	0.17
48 ≤ < 51	38.2	39.9	39.2	25.0	32.6	44.7	38.1	
51 ≤ < 54	28.8	25.3	34.0	37.5	32.6	25.5	29.1	
54 ≤	17.4	18.7	18.6	12.5	16.7	10.6	12.4	
Missing	1.2	1.1	1.0	0.0	2.1	0.0	3.1	
Parity number (%)								
0	10.1	12.4	7.4	4.8	6.2	12.1	8.0	< 0.01
1	11.0	10.5	9.3	19.1	13.4	8.1	9.3	
2	44.8	44.7	44.4	57.1	45.3	42.4	41.1	
3 ≤	26.2	24.8	29.0	9.5	28.2	28.3	32.6	
Missing	7.9	7.6	9.9	9.5	6.9	9.1	9.0	
Age at first birth among parous women (%)								
≤ 24	34.2	37.4	43.3	5.6	42.6	43.6	47.4	< 0.01
25 ≤ ≤ 29	39.0	46.7	42.5	72.2	44.2	46.1	42.4	
30 ≤ ≤ 50	10.7	13.3	12.7	16.6	11.7	6.4	8.0	
Missing	16.2	2.6	1.5	5.6	1.5	3.9	2.2	
Use of exogenous female hormone or oral contraceptives (%)								
Never	81.7	81.8	80.3	90.4	83.6	75.8	78.0	< 0.01
Ever	10.0	9.7	11.7	4.8	9.5	12.1	9.3	
Missing	8.3	8.5	8.0	4.8	6.9	12.1	12.7	
Family history of breast cancer in first-degree relatives (%)								
No	90.0	90.9	87.6	80.9	88.5	94.9	95.8	< 0.01
Yes	10.0	9.1	12.4	19.1	11.5	5.1	4.2	
Pack-years of smoking (%)								
Never	81.1	81.2	79.6	76.2	82.0	80.8	81.6	0.36
0 < ≤13	6.6	6.9	7.4	14.2	5.2	6.0	7.4	
13 <	7.8	7.6	6.2	4.8	9.2	8.1	6.9	
Missing	4.5	4.3	6.8	4.8	3.6	5.1	4.1	
Alcohol drinking (%)								
Never	72.2	69.1	79.6	81.0	71.8	80.8	73.9	0.33
Past	3.1	2.7	4.3	0.0	3.3	4.0	2.5	
Current	24.7	28.2	16.1	19.0	24.9	15.2	23.6	
Dietary intake (mean ± SD)								
Folate intake (μg per day)[c]	214.4 ± 72.6	213.9 ± 76.0	217.0 ± 67.7	185.4 ± 54.4	210.7 ± 68.6	231.1 ± 70.0	219.6 ± 84.0	0.06
Energy intake (kcal per day)	1203.3 ± 274.7	1186.1 ± 280.0	1226.8 ± 273.6	1200.3 ± 228.8	1230.1 ± 258.4	1198.7 ± 293.1	1204.7 ± 275.6	0.88

[a]Menopause was defined as the cessation of menstrual periods due to natural or other reasons including surgery.

[b]Household wife/domestic help.

[c]Energy-adjusted intake.

[d]P for total cases versus controls, which were from t-test for continuous variables and chi-square test for categorical variables.

Table 2. Odds ratio (OR) in relation to alcohol intake according to menopausal status.

	Total[a]					Premenopausal[b]					Postmenopausal[c]				
	Controls	Cases	OR	95% CI	*P*	Controls	Cases	OR	95% CI	*P*	Controls	Cases	OR	95% CI	*P*
History of alcohol drinking															
Never	2168	907	1 (Reference)			514	257	1 (Reference)			1549	606	1 (Reference)		
Past	73	39	1.11	0.73 - 1.69		24	12	1.02	0.46 - 2.24		49	23	1.13	0.65 - 1.96	
Current	692	310	0.93	0.79 - 1.11		346	169	1.04	0.80 - 1.36		300	120	0.82	0.64 - 1.06	
Ever	765	349	0.96	0.81 - 1.12		370	181	1.04	0.80 - 1.36		346	143	0.86	0.68 - 1.09	
Age at the start of drinking (years)															
Never	2168	907	1 (Reference)			514	257	1 (Reference)			1549	606	1 (Reference)		
25 <	205	94	1.12	0.85 - 1.46		36	27	1.67	0.93 - 2.98		159	62	0.98	0.71 - 1.36	
20 < ≤ 25	96	57	1.25	0.88 - 1.79		38	28	1.70	0.97 - 3.00		52	25	0.81	0.48 - 1.37	
≤ 20	376	168	0.84	0.67 - 1.05		265	116	0.90	0.67 - 1.23		83	39	0.76	0.50 - 1.16	
P for trend					0.31					0.77					0.17
Frequency of drinking															
Never	2168	907	1 (Reference)			514	257	1 (Reference)			1549	606	1 (Reference)		
Occasinoal	212	86	0.80	0.60 - 1.06		128	54	0.93	0.63 - 1.38		73	26	0.68	0.42 - 1.12	
1-2 per week	166	74	0.96	0.71 - 1.29		81	35	0.94	0.59 - 1.49		72	34	1.02	0.66 - 1.59	
3-4 per week	169	84	1.04	0.78 - 1.40		82	41	1.09	0.70 - 1.71		77	36	1.01	0.66 - 1.57	
5-7 per week	185	85	0.94	0.70 - 1.26		74	46	1.18	0.74 - 1.87		98	33	0.65	0.42 - 1.01	
P for trend					0.79					0.53					0.14
Amount of alcohol consumed per occasion															
Never	2168	907	1 (Reference)			514	257	1 (Reference)			1549	606	1 (Reference)		
< 15.0 g	387	156	0.82	0.66 - 1.02		185	84	0.95	0.68 - 1.33		174	61	0.73	0.53 - 1.01	
15.0 ≤ < 30.0 g	212	114	1.15	0.89 - 1.50		102	55	1.16	0.77 - 1.74		97	51	1.07	0.73 - 1.57	
30.0 ≤ < 50.0 g	99	41	0.88	0.60 - 1.32		56	22	0.89	0.50 - 1.60		40	16	0.80	0.42 - 1.5	
≥ 50.0 g	36	18	0.94	0.51 - 1.75		25	13	1.01	0.46 - 2.21		8	3	0.65	0.16 - 2.75	
P for trend					0.83					0.93					0.35
Amount of alcohol consumed per day															
Never	2168	907	1 (Reference)			514	257	1 (Reference)			1549	606	1 (Reference)		
< 5.0 g	341	147	0.89	0.71 - 1.11		187	79	0.92	0.65 - 1.29		130	58	0.92	0.65 - 1.30	
5.0 ≤ < 15.0 g	236	100	0.88	0.68 - 1.14		115	49	0.90	0.60 - 1.36		111	42	0.77	0.52 - 1.15	
15.0 ≤ < 30.0 g	84	42	1.04	0.69 - 1.56		33	25	1.49	0.80 - 2.77		43	16	0.73	0.39 - 1.37	
≥ 30.0 g	60	33	1.13	0.71 - 1.82		30	18	1.18	0.59 - 2.37		26	11	0.78	0.36 - 1.69	
P for trend					0.80					0.59					0.12

[a]Adjusted by age (continuous), BMI (< 18.5, 18.5 ≤ < 25.0, 25.0 ≤ < 30.0, 30.0 ≤), occupation (household wife/domestic help, administrative, industrial, agricultural, other), physical activity (almost no, more than one hour per week), menopausal status (premenopausal, postmenopausal), age at menarche (≤ 12, 13, 14, 15 ≤), age at first birth (≤ 24, 25 ≤ ≤ 29, 30 ≤ ≤ 50), family history of breast cancer in first-degree relatives (yes, no), parity number (0, 1, 2, 3 ≤), use of exogenous female hormone or oral contraceptives (yes, no), referrel status (from screening, other), year of recruitment (continuous), area of residence (southern Miyagi prefecture, other area), packyears of smoking (0, 0 < ≤ 13, 13 <) and intake of folate (tertiles) and energy (tertiles).

[b]Adjusted by age (continuous), BMI (< 18.5, 18.5 ≤ < 25.0, 25.0 ≤ < 30.0, 30.0 ≤), occupation (household wife/domestic help, administrative, industrial, agricultural, other), physical activity (almost no, more than one hour per week), age at menarche (≤ 12, 13, 14, 15 ≤), age at first birth (≤ 24, 25 ≤ ≤ 29, 30 ≤ ≤ 50), family history of breast cancer in first-degree relatives (yes, no), parity number (0, 1, 2, 3 ≤), use of exogenous female hormone or oral contraceptives (yes, no), referrel status (from screening, other), year of recruitment (continuous), area of residence (southern Miyagi prefecture, other area), packyears of smoking (0, 0 < ≤13, 13 <) and intake of folate (tertiles) and energy (tertiles).

[c]Adjusted by age (continuous), BMI (< 18.5, 18.5 ≤ < 25.0, 25.0 ≤ < 30.0, 30.0 ≤), occupation (household wife/domestic help, administrative, industrial, agricultural, other), physical activity (almost no, more than one hour per week), age at menopause (< 48, 48 ≤ < 51, 51 ≤ < 54, 54 ≤), age at menarche (≤ 12, 13, 14, 15 ≤), age at first birth (≤ 24, 25 ≤ ≤ 29, 30 ≤ ≤ 50), family history of breast cancer in first-degree relatives (yes, no), parity number (0, 1, 2, 3 ≤), use of exogenous female hormone or oral contraceptives (yes, no), referrel status (from screening, other), year of recruitment (continuous), area of residence (southern Miyagi prefecture, other area), packyears of smoking (0, 0 < ≤ 13, 13 <) and intake of folate (tertiles) and energy (tertiles).

drinking was statistically significant (OR = 0.63, 95% CI: 0.41-0.95). Furthermore, a significantly decreased risk for start of drinking at an early age (20 years old or less) was observed for ER+/PgR− cancer (OR = 0.43, 95% CI: 0.22-0.84). Analyses of the frequency of drinking, amount of alcohol consumed per occasion and that consumed per day also demonstrated a significant inverse association between these exposure variables and the risk of ER+/PgR− cancer. For ER−/PgR+ cancer, similar inverse associations were observed for most of the alcohol-related measures. However, the risk for each category was not fully evaluated because of the limited number of cases.

Table 4 shows the results of analysis stratified according to some potential factors. In this analysis, we did not include the risk evaluation for ER−/PgR+ because of the small number of cases. In terms of menopausal status, ever-drinking and higher alcohol consumption were positively associated with the risk of premenopausal ER+/PgR+ and ER−/PgR− cancer, but these associations were non-significant. For premenopausal ER+/PgR−, a strong inverse association between alcohol consumption and breast cancer risk was observed (*P* for trend = 0.01). Heterogeneity test across the three receptor types also demonstrated a significant difference (*P* for heterogeneity = 0.02). Among post-

Table 3. Odds ratio (OR) in relation to alcohol intake according to hormone receptor status.

		ER+/PgR+				ER+/PgR−				ER−/PgR+				ER−/PgR−			
	Controls	Cases	OR	95% CI	*P*	Cases	OR	95% CI	*P*	Cases	OR	95% CI	*P*	Cases	OR	95% CI	*P*
History of alcohol drinking																	
Never	2168	462	1 (Reference)			129	1 (Reference)			17	1 (Reference)			219	1 (Reference)		
Past	73	18	0.99	0.57 - 1.73		7	1.31	0.57 - 3.05		0	-	- - -		10	1.26	0.62 - 2.55	
Current	692	189	1.10	0.89 - 1.36		26	0.55	0.35 - 0.87		4	0.48	0.15 - 1.55		76	1.01	0.75 - 1.36	
Ever	765	207	1.09	0.89 - 1.34		33	0.63	0.41 - 0.95		4	0.44	0.14 - 1.42		86	1.04	0.78 - 1.38	
Age at the start of drinking (years)																	
Never	2168	462	1 (Reference)			129	1 (Reference)			17	1 (Reference)			219	1 (Reference)		
25 <	205	50	1.27	0.90 - 1.79		12	0.80	0.43 - 1.51		1	0.52	0.06 - 4.19		26	1.21	0.77 - 1.89	
20 < ≤ 25	96	36	1.59	1.04 - 2.43		5	0.71	0.28 - 1.83		0	-	- - -		13	1.25	0.67 - 2.32	
≤ 20	376	107	0.97	0.74 - 1.28		11	0.43	0.22 - 0.84		2	0.40	0.08 - 1.98		39	0.91	0.61 - 1.35	
P for trend					0.63				0.01				0.18				0.89
Frequency of drinking																	
Never	2168	462	1 (Reference)			129	1 (Reference)			17	1 (Reference)			219	1 (Reference)		
Occasinoal	212	58	1.01	0.72 - 1.41		8	0.59	0.28 - 1.24		0	-	- - -		15	0.64	0.36 - 1.12	
1-2 per week	166	44	1.08	0.75 - 1.56		3	0.28	0.09 - 0.91		2	0.92	0.19 - 4.40		23	1.35	0.84 - 2.16	
3-4 per week	169	50	1.23	0.86 - 1.75		7	0.58	0.26 - 1.30		0	-	- - -		23	1.23	0.76 - 1.98	
5-7 per week	185	47	1.05	0.73 - 1.52		10	0.69	0.34 - 1.39		2	0.95	0.20 - 4.60		20	0.93	0.56 - 1.55	
P for trend					0.41				0.04				0.49				0.64
Amount of alcohol consumed per occasion																	
Never	2168	462	1 (Reference)			129	1 (Reference)			17	1 (Reference)			219	1 (Reference)		
< 15.0 g	387	93	0.94	0.72 - 1.23		17	0.64	0.37 - 1.10		3	0.60	0.16 - 2.23		36	0.83	0.57 - 1.22	
15.0 ≤ < 30.0 g	212	73	1.45	1.06 - 1.98		10	0.67	0.34 - 1.33		1	0.39	0.05 - 3.12		25	1.14	0.72 - 1.81	
30.0 ≤	135	32	0.93	0.60 - 1.45		2	0.20	0.05 - 0.84		0	-	- - -		20	1.33	0.78 - 2.28	
P for trend					0.32				0.01				0.13				0.41
Amount of alcohol consumed per day																	
Never	2168	462	1 (Reference)			129	1 (Reference)			17	1 (Reference)			219	1 (Reference)		
< 5.0 g	341	93	1.05	0.80 - 1.39		11	0.50	0.26 - 0.96		2	0.44	0.09 - 2.04		35	0.97	0.65 - 1.43	
5.0 ≤ < 15.0 g	236	56	0.95	0.69 - 1.33		10	0.58	0.29 - 1.15		1	0.37	0.05 - 2.97		27	1.03	0.66 - 1.60	
15.0 ≤	144	44	1.29	0.87 - 1.91		7	0.63	0.28 - 1.45		1	0.63	0.08 - 5.31		18	1.07	0.62 - 1.85	
P for trend					0.42				0.04				0.29				0.85

All models were adjusted by age (continuous), BMI (< 18.5, 18.5 ≤ < 25.0, 25.0 ≤ < 30.0, 30.0 ≤), occupation (household wife/domestic help, administrative, industrial, agricultural, other), physical activity (almost no, more than one hour per week), menopausal status (premenopausal, postmenopausal), age at menarche (≤ 12, 13, 14, 15 ≤), age at first birth (≤ 24, 25 ≤ ≤ 29, 30 ≤ ≤ 50), family history of breast cancer in first-degree relatives (yes, no), parity number (0, 1, 2, 3 ≤), use of exogenous female hormone or oral contraceptives (yes, no), referrel status (from screening, other), year of recruitment (continuous), area of residence (southern Miyagi prefecture, other area), packyears of smoking (0, 0 < ≤ 13, 13 <) and intake of folate (tertiles) and energy (tertiles).

menopausal women, alcohol consumption was not associated with breast cancer risk for any hormone receptor status. Analysis according to BMI (< 25.0, ≥ 25.0) showed that ever-drinking was significantly associated with a lower risk of ER+/PgR− cancer in the high BMI group. With regard to folate intake, no significant association between alcohol consumption and breast cancer risk was observed in any subgroup, except for a risk of ER+/PgR− in subjects with low folate intake. With regard to exogenous hormone use, the direction of the risk associated with alcohol consumption was similar between never and ever users, regardless of hormone receptor status, although the risk of ER+/PgR− cancer among ever users was not fully evaluated.

As for the risk posed by the amount of alcohol consumed per day, we attempted additional analysis based on quartile cut-off points. Although the data are not shown in the tables, the results of this additional analysis were similar to those based on arbitrary cut-off points. The inverse association between the amount of alcohol consumed per day and the risk of ER+/PgR− cancer shown in Table 3 was also found in the additional analysis (*P* for trend = 0.02), supporting the linear inverse trend between alcohol intake and cancer risk.

Discussion

This hospital-based case-control study was designed to clarify the association between alcohol consumption and breast cancer risk in relation to menopausal and joint hormone receptor status.

Prior to the analysis of hormone receptor status, our data for women overall indicated no association between alcohol-related measures and breast cancer risk. A similar result was obtained when analysis was conducted according to menopausal status. These findings were comparable to those of our previous cohort study (Kawai et al. 2011). However, inconsistency has been observed among the results of previous Japanese studies. A qualitative review of such Japanese studies, including three cohort studies and eight case-control studies, found an increased risk among drinkers in three of them (Kato et al. 1989; Hirose et al. 1995; Lin et al. 2005), whereas the remaining studies found no such risk elevation. Subsequent studies including the Japan Public Health Center-based Prospective Study (JPHC Study) (Suzuki et al. 2010) and a case-control study conducted in Aichi (Islam et al. 2013) demonstrated a positive association between alcohol drinking and breast cancer risk. On the other hand, some previous epidemiological studies including those targeting Asian-American or Chinese women (Li et al. 2011; Zhang and Holman 2011; Wu et al. 2012) have shown an inverse association or no association between alcohol consumption and breast cancer risk. Although alcohol consumption has been regarded as an established risk factor for breast cancer in Western countries, it is likely that overall breast cancer risk in relation to

Table 4. Odds ratio (OR) in relation to alcohol intake according to hormone receptor status within strara of potential risk factors.

		ER+/PgR+				ER+/PgR−				ER−/PgR−				*P* for
	Controls	Cases	OR	95% CI	*P*	Cases	OR	95% CI	*P*	Cases	OR	95% CI	p	heterogeneity[f]
Menopausal status														
Premenopausal[a]														
Never	514	153	1 (Reference)			28	1 (Reference)			54	1 (Reference)			
Ever	370	124	1.23	0.89 - 1.68		7	0.32	0.13 - 0.78		40	1.20	0.75 - 1.92		0.01
Amount of alcohol consumed per day														
0 < <5.0 g	187	57	1.15	0.77 - 1.71		5	0.49	0.18 - 1.34		14	0.85	0.45 - 1.63		
5.0 ≤ <15.0 g	115	31	0.97	0.60 - 1.59		1	0.13	0.02 - 1.03		15	1.40	0.73 - 2.70		
15.0 g ≤	63	28	1.45	0.82 - 2.58		1	0.24	0.03 - 1.90		9	1.54	0.66 - 3.59		
P for trend					0.35				0.01				0.24	0.02
Postmenopausal[b]														
Never	1549	289	1 (Reference)			97	1 (Reference)			153	1 (Reference)			
Ever	346	73	0.99	0.73 - 1.36		24	0.75	0.46 - 1.24		37	0.88	0.58 - 1.31		0.6
Amount of alcohol consumed per day														
0 < < 5.0 g	130	32	1.12	0.73 - 1.74		5	0.44	0.17 - 1.12		18	1.14	0.66 - 1.96		
5.0 ≤ < 15.0 g	111	21	0.88	0.52 - 1.47		9	0.86	0.40 - 1.83		9	0.64	0.31 - 1.32		
15.0 g ≤	69	14	0.94	0.49 - 1.81		5	0.67	0.25 - 1.83		7	0.73	0.31 - 1.70		
P for trend					0.79				0.25				0.28	0.59
Body mass index[c]														
< 25.0														
Never	1490	277	1 (Reference)			88	1 (Reference)			149	1 (Reference)			
Ever	567	154	1.17	0.91 - 1.49		27	0.72	0.44 - 1.15		68	1.18	0.85 - 1.63		0.15
Amount of alcohol consumed per day														
0 < <5.0 g	250	71	1.15	0.84 - 1.58		9	0.59	0.29 - 1.23		27	1.09	0.69 - 1.71		
5.0 ≤ < 15.0 g	185	42	0.94	0.64 - 1.38		8	0.60	0.28 - 1.29		22	1.12	0.68 - 1.85		
15.0 g ≤	108	33	1.43	0.90 - 2.26		6	0.75	0.30 - 1.87		13	1.07	0.56 - 2.04		
P for trend					0.30				0.15				0.64	0.19
≥ 25.0														
Never	661	184	1 (Reference)			41	1 (Reference)			69	1 (Reference)			
Ever	191	51	0.83	0.56 - 1.23		6	0.38	0.15 - 0.97		18	0.76	0.42 - 1.37		0.30
Amount of alcohol consumed per day														
0 < <5.0 g	86	21	0.74	0.42 - 1.30		2	0.28	0.06 - 1.26		8	0.72	0.31 - 1.65		
5.0 ≤ <15.0 g	49	13	0.87	0.44 - 1.73		2	0.50	0.11 - 2.27		5	0.83	0.30 - 2.26		
15.0 g ≤	36	11	0.95	0.43 - 2.09		1	0.32	0.04 - 2.59		5	1.17	0.40 - 3.48		
P for trend					0.59				0.09				0.87	0.33
Folate intake[d]														
< 214.4 μg per day														
Never	1021	233	1 (Reference)			60	1 (Reference)			109	1 (Reference)			
Ever	446	118	1.03	0.78 - 1.36		16	0.52	0.28 - 0.95		54	1.12	0.77 - 1.63		0.08
Amount of alcohol consumed per day														
0 < < 5.0 g	211	48	0.90	0.62 - 1.31		5	0.39	0.15 - 1.02		23	1.11	0.67 - 1.82		
5.0 ≤ < 15.0 g	129	35	1.05	0.69 - 1.61		4	0.44	0.15 - 1.27		17	1.19	0.68 - 2.11		
15.0 g ≤	90	30	1.22	0.74 - 1.99		4	0.54	0.18 - 1.63		12	1.06	0.53 - 2.11		
P for trend					0.56				0.05				0.63	0.09
≥ 214.4 μg per day														
Never	1147	229	1 (Reference)			69	1 (Reference)			110	1 (Reference)			
Ever	319	89	1.14	0.84 - 1.56		17	0.75	0.42 - 1.35		32	0.98	0.62 - 1.53		0.41
Amount of alcohol consumed per day														
0 < < 5.0 g	130	45	1.33	0.89 - 2.00		6	0.67	0.28 - 1.61		12	0.86	0.45 - 1.65		
5.0 ≤ < 15.0 g	107	21	0.82	0.48 - 1.39		6	0.73	0.30 - 1.78		10	0.91	0.45 - 1.86		
15.0 g ≤	54	14	1.24	0.64 - 2.40		3	0.84	0.24 - 2.94		6	1.03	0.41 - 2.59		
P for trend					0.74				0.41				0.83	0.65
Exogenous houmone use[e]														
Never user														
Never	1692	379	1 (Reference)			104	1 (Reference)			185	1 (Reference)			
Ever	597	168	1.08	0.86 - 1.36		26	0.62	0.39 - 0.98		70	1.07	0.78 - 1.46		0.08
Amount of alcohol consumed per day														
0 < <5.0 g	275	74	1.02	0.75 - 1.38		6	0.33	0.14 - 0.77		25	0.84	0.53 - 1.32		
5.0 ≤ < 15.0 g	188	48	1.01	0.70 - 1.44		10	0.70	0.35 - 1.40		23	1.09	0.67 - 1.76		
15.0 g ≤	104	36	1.35	0.87 - 2.09		5	0.67	0.25 - 1.74		16	1.40	0.77 - 2.53		
P for trend					0.34				0.08				0.43	0.10
Ever user														
Never	161	36	1 (Reference)			14	1 (Reference)			16	1 (Reference)			
Ever	112	29	1.27	0.63 - 2.58		5	0.53	0.13 - 2.05		13	1.40	0.56 - 3.47		0.45
Amount of alcohol consumed per day														
0 < < 5.0 g	43	16	1.99	0.84 - 4.68		4	1.26	0.28 - 5.61		7	2.00	0.67 - 5.96		
5.0 ≤ < 15.0 g	33	5	0.43	0.13 - 1.50		0	-	- - -		4	1.18	0.32 - 4.39		
15.0 g ≤	33	6	1.34	0.38 - 4.78		1	0.27	0.02 - 3.07		2	0.71	0.13 - 3.95		
P for trend					0.87				0.14				0.97	0.40

alcohol intake varies among different ethnic groups and different regions.

Our analysis according to hormone receptor status demonstrated a difference in breast cancer risk associated with alcohol consumption between concordant and discordant receptor subtypes. For concordant receptor subtypes, no association was observed between alcohol consumption and breast cancer risk. Conversely, a significantly lower risk of breast cancer associated with ever-drinking was observed for discordant subtype. With regard to hormone receptor-specific risk, a meta-analysis has indicated that alcohol consumption was associated with a significantly increased risk of ER+/PgR+ and ER+/PgR− cancer (Suzuki et al. 2008). However, there have been variations in receptor-specific risk among recent studies. For example, the JPHC Study conducted in Japan demonstrated an increased risk of ER+/PgR+ cancer among heavy drinkers (> 150 g of ethanol per week); however, the trend test showed non-significance (Suzuki et al. 2010). In the cohort study conducted by the National Institutes of Health (NIH), alcohol consumption was significantly and positively associated with the risk of ER+/PgR+ cancer; however, the relative risks for ER+/PgR− and ER−/PgR− were non-significant (Lew et al. 2009). A Chinese case-control study found that postmenopausal women who had consumed an average of ≥15 g alcohol/day had a markedly higher risk of discordant subtype, i.e., ER+/PgR− or ER−/PgR+ (Zhang and Holman 2011). No such risk elevation was observed for concordant subtypes including ER+/PgR+ and ER−/PgR− (Zhang and Holman 2011). The inconsistency of overall breast cancer risk among previous studies mentioned above may be due to the difference in receptor-specific risk and variations in hormone receptor status among study populations.

We interpreted the difference in receptor-specific risk among study populations including ours as follows. First, as mentioned above, the risk of the discordant type in relation to alcohol intake was extremely large in postmenopausal Chinese women (Zhang and Holman 2011), being contrary to our findings. Such a positive association of alcohol consumption with the risk of ER+/PgR− cancer has also been observed in some previous studies from Western countries. The difference in the risk of ER+/PgR− cancer among regions and races suggests that alcohol-related breast cancer risk may reflect not only the direct biologic effects of alcohol but also the distributions of other risk factors and sociocultural background. For example, our previous case-control study showed that the associations of established breast cancer risk factors including reproductive and anthropometric factors with the risk of ER+/PgR− cancer were weak or unity, suggesting that the epidemiologic characteristics of ER+/PgR− cancer may differ from those of other receptor subtypes (Kawai et al. 2012, 2013). The characteristics of cases and controls shown in Table 1 also suggest such a difference. Furthermore, the analysis stratified according to menopausal status in the present study showed that the inverse association between alcohol consumption and the risk of ER+/PgR− cancer was limited to premenopausal women (Table 4), despite the fact that cases with ER+/PgR− tended to be older than those in the other receptor groups. Japanese women, especially premeno-

[a]Adjusted by age (continuous), BMI (< 18.5, 18.5 ≤ < 25.0, 25.0 ≤ < 30.0, 30.0 ≤), occupation (household wife/domestic help, administrative, industrial, agricultural, other), physical activity (almost no, more than one hour per week), age at menarche (≤ 12, 13, 14, 15 ≤), age at first birth (≤ 24, 25 ≤ ≤ 29, 30 ≤ ≤ 50), family history of breast cancer in first-degree relatives (yes, no), parity number (0, 1, 2, 3 ≤), use of exogenous female hormone or oral contraceptives (yes, no), referrel status (from screening, other), year of recruitment (continuous), area of residence (southern Miyagi prefecture, other area), packyears of smoking (0, 0 < ≤ 13, 13 <) and intake of folate (tertiles) and energy (tertiles).

[b]Adjusted by age (continuous), BMI (< 18.5, 18.5 ≤ < 25.0, 25.0 ≤ < 30.0, 30.0 ≤), occupation (household wife/domestic help, administrative, industrial, agricultural, other), physical activity (almost no, more than one hour per week), age at menopause (< 48, 48 ≤ < 51, 51 ≤ < 54, 54 ≤), age at menarche (≤ 12, 13, 14, 15 ≤), age at first birth (≤ 24, 25 ≤ ≤ 29, 30 ≤ ≤ 50), family history of breast cancer in first-degree relatives (yes, no), parity number (0, 1, 2, 3 ≤), use of exogenous female hormone or oral contraceptives (yes, no), referrel status (from screening, other), year of recruitment (continuous), area of residence (southern Miyagi prefecture, other area), packyears of smoking (0, 0 < ≤ 13, 13 <) and intake of folate (tertiles) and energy (tertiles).

[c]Adjusted by age (continuous), occupation (household wife/domestic help, administrative, industrial, agricultural, other), physical activity (almost no, more than one hour per week), menopausal status (premenopausal, postmenopausal), age at menarche (≤ 12, 13, 14, 15 ≤), age at first birth (≤ 24, 25 ≤ ≤ 29, 30 ≤ ≤ 50), family history of breast cancer in first-degree relatives (yes, no), parity number (0, 1, 2, 3 ≤), use of exogenous female hormone or oral contraceptives (yes, no), referrel status (from screening, other), year of recruitment (continuous), area of residence (southern Miyagi prefecture, other area), packyears of smoking (0, 0 < ≤ 13, 13 <) and intake of folate (tertiles) and energy (tertiles).

[d]Adjusted by age (continuous), BMI (< 18.5, 18.5 ≤ < 25.0, 25.0 ≤ < 30.0, 30.0 ≤), occupation (household wife/domestic help, administrative, industrial, agricultural, other), physical activity (almost no, more than one hour per week), menopausal status (premenopausal, postmenopausal), age at menarche (≤ 12, 13, 14, 15 ≤), age at first birth (≤ 24, 25 ≤ ≤ 29, 30 ≤ ≤ 50), family history of breast cancer in first-degree relatives (yes, no), parity number (0, 1, 2, 3 ≤), use of exogenous female hormone or oral contraceptives (yes, no), referrel status (from screening, other), year of recruitment (continuous), area of residence (southern Miyagi prefecture, other area) and packyears of smoking (0, 0 < ≤ 13, 13<).

[e]Adjusted by age (continuous), BMI (< 18.5, 18.5 ≤ < 25.0, 25.0 ≤ < 30.0, 30.0 ≤), occupation (household wife/domestic help, administrative, industrial, agricultural, other), physical activity (almost no, more than one hour per week), menopausal status (premenopausal, postmenopausal), age at menarche (≤ 12, 13, 14, 15 ≤), age at first birth (≤ 24, 25 ≤ ≤ 29, 30 ≤ ≤ 50), family history of breast cancer in first-degree relatives (yes, no), parity number (0, 1, 2, 3 ≤), referrel status (from screening, other), year of recruitment (continuous), area of residence (southern Miyagi prefecture, other area), packyears of smoking (0, 0 < ≤ 13, 13 <) and intake of folate (tertiles) and energy (tertiles).

[f]Test for heterogeneity of P values between the 3 hormone receptor types.

pausal women with ER+/PgR− cancer, may have specific characteristics related to alcohol consumption, which may be responsible for the reduced risk. Second, most studies from Western countries have demonstrated a positive association between alcohol consumption and the risk of ER+/PgR+ cancer. The present study also demonstrated a slightly increased risk for ER+/PgR+ cancer among women who consumed alcohol of ≥15 g/day (OR = 1.29); statistically, however, this was not significant. Our study subjects tended to consume less alcohol than those in Western or Asian studies. The present study would not have been able to detect a small risk in relation to alcohol consumption because of insufficient statistical power. Regarding the direct biologic effects of alcohol on breast cancer risk, one widely discussed hypothesis is that alcohol may have some effects on circulating estrogen levels. Although we could not define biological mechanisms explaining the difference in alcohol-related risk between discordant and concordant subtype, it is likely that such an alcohol dependent-mechanism would affect the growth of ER+/PgR+ cancer (Purohit 2000; Dorgan et al. 2001). Acetaldehyde, a metabolite of ethanol, may have direct carcinogenic effects (Scoccianti et al. 2014). Third, the types of alcohol beverages consumed might also have affected the receptor-specific risk (Scoccianti et al. 2014). In our study, approximately 75% of ever drinkers among the controls drank beer (data not shown in tables). This frequency differed from not only those in American and European populations (Allen et al. 2009; Li et al. 2009) but also that in the Japanese population (Suzuki et al. 2010). In the JHPC study population, the proportion of beer drinkers was low, whereas beverages containing high level of alcohol such as *sake* and *shochu* were preferably consumed (Suzuki et al. 2010). Alcoholic beverages contain several chemicals, and it is possible that these chemicals may have different effects on receptor-specific risk (Scoccianti et al. 2014).

The present study had both strengths and limitations. First, we considered comparability between the cases and the controls (Schlesselman 1982; Rothman and Greenland 1998). We selected the controls from among patients admitted to the same hospital as the cases. To improve comparability between the cases and controls, we appropriately controlled for the background characteristics such as area of residence and referral status in the statistical analysis. Furthermore, patients with alcohol-related diseases were excluded from among the controls. Consequently, the distribution in the history of alcohol drinking among control subjects was almost the same as that of women in the Miyagi cohort covering the catchment area of the present study (Kawai et al. 2011). Second, the problem of limited statistical power must be considered in the analysis of ER−/PgR+ cancer. The results for this receptor type might have been inconclusive due to the small number of cases. Further studies will be needed to confirm the risk for ER−/PgR+ cancer. Third, it is necessary to evaluate the possibility of information bias. Self-reported information on exposure might have been vulnerable to misclassification. Nevertheless, as any such misclassification would have been non-differential, this bias is unlikely to have distorted the present results. Fourth, it is possible that the background characteristics of the study subjects might have been changed because the recruitment period ranged over a long period of more than 10 years (1997-2011). In particular, as well as the generalized habit of alcohol drinking, the number of current drinkers and the amounts of alcohol being consumed have been increasing among women (Ministry of Health, Labour and Welfare 2017). Therefore, we performed additional analyses by dividing the data into two periods (1997-2003, 2004-2011). However, the ORs for alcohol-related items were similar between the two periods (data not shown in tables).

One of the strengths of our study was the low rate of missing data (7.9%) for hormone receptor status. Compared with our study, the rates of missing data in some previous studies, including cohort studies, were relatively high. There is some difficulty in collecting information on receptor status in Japanese population-based cohort studies (Lin et al. 2005; Suzuki et al. 2010; Kawai et al. 2011). Therefore, hospital-based studies would be more suitable for assessment of breast cancer risk according to hormone receptor status. The other strength of this study was its high participation rates: 94.4% for cases and 89.6% for controls, thus increasing its reliability.

Using the OR for ever-drinking, we attempted to calculate the population attributable fraction (PAF) (Miettinen 1974). In terms of the PAF, 12% of ER+/PgR− cancers could have been prevented by alcohol intake (data not shown in tables). However, the frequency of ER+/PgR− cancer is lower than that of concordant receptor subtypes. Alcohol drinking is associated with increased risks for various diseases (Inoue et al. 2012), and may be related to the increased risk of breast cancer with concordant subtypes. Therefore, we should avoid emphasizing that alcohol intake reduces the risk of breast cancer with discordant receptor. We consider that the present findings provide a clue for elucidating the etiology of breast cancer rather than for preventing discordant subtype.

In conclusion, the present case-control study has shown that alcohol intake had no overall effect on breast cancer risk for any concordant hormone receptor status (ER+/PgR+, ER−/PgR−), whereas an inverse association was observed between alcohol intake and the risk of discordant hormone receptor subtypes (ER+/PgR−, ER−/PgR+). In terms of menopausal status, this inverse association with alcohol intake was found only for premenopausal ER+/PgR− cancer, despite the fact that cases with ER+/PgR− tended to be older. Japanese women with discordant hormone receptor (ER+/PgR−, ER−/PgR+) breast cancer may have unique characteristics that are responsible for the inverse association with alcohol drinking. These results may be important in terms of elucidating the etiology of breast cancer. Further studies are needed to clarify the

association between alcohol consumption and breast cancer risk.

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Conflict of Interest

The authors declare no conflict of interest.

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