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ORIGINAL ARTICLE

Association between alcohol consumption and mammographic density: a hospital-based cross-sectional study

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Abstract

Background Mammographic density (MD), the proportion of radiological dense breast, has been reported to be a strong risk factor for breast cancer in many studies. Epidemiological evidence indicates that alcohol consumption increases the risk of breast cancer. In Western countries, a positive association between alcohol consumption and MD has been reported.

Methods To investigate the effect of alcohol consumption on MD, we conducted a cross-sectional analysis of healthy women enrolled in a breast cancer screening program at the Ebina Health Service Center, Japan, in 2012, comprising 477 premenopausal women and 308 postmenopausal women. Alcohol consumption was assessed using a self-report questionnaire. Unconditional logistic regression was applied to calculate the odds ratio (OR) and 95% confidence intervals (CI) while adjusting for confounders.

Results The study included 497 women with high breast density (HD group) and 288 women with low breast density (LD group). In all women, multivariate analysis revealed that the OR for HD was significantly increased among women with the highest alcohol intake (≥ 140 g/week of ethanol) compared with abstainers (OR 2.1, 95% CI 1.2–3.9 $p = 0.01$). The linear trend with increasing alcohol consumption was statistically significant ($p = 0.009$).

Conclusion MD was positively associated with alcohol consumption in Japanese women.

Keywords Mammographic density · Alcohol consumption

Introduction

Mammographic breast density (MD) is a reflection of the amount of fat, connective, and epithelial tissue in the breast [1]. Irrespective of ethnicity, epidemiologic studies have demonstrated that elevated MD is a strong risk factor for breast cancer [2, 3]. Boyd et al. reported that women within the highest categories of MD have a four–sixfold increased risk compared to women within the lowest categories [2]. MD was also associated with breast cancer risk in Japanese and Chinese women [3, 4].

Japan has recently experienced an increase in breast cancer incidence rates, which are currently low compared with those in Western countries [5]. Although breast cancer risk factors are likely to be common to women of all ethnicities, there are many differences in diet, genetics, obesity, and other breast cancer risk factors between Caucasian and Japanese women.

A number of studies have evaluated the association between MD and breast cancer risk factors. MD is inversely associated with older age, parity, and body mass index (BMI) [6, 7]. However, most previous studies evaluating the association were conducted among women in Western countries. A few studies have examined the association between MD and breast cancer risk factors among East Asian women [8, 9] and these results from these studies are consistent with that of studies conducted in Western Countries. In Japan, BMI and parity were reported to be significantly associated with MD [10, 11].

High alcohol consumption has consistently been associated with an increased risk of breast cancer in Western countries and in Japan [12, 13]. A number of studies conducted in Western countries reported a positive association between alcohol consumption and MD in both pre- and postmenopausal women [14, 15]. Recently, it was suggested that alcohol consumption was not associated with MD in mainland China [8]. However, conclusive

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results have not been drawn from this research since details related to alcohol consumption were not included. Moreover, there are no previous reports on the association between MD and alcohol consumption among Japanese women.

A positive family history of breast cancer (FHBC) is a widely recognized breast cancer risk factor, although the association between MD and FHBC remains controversial [16]. A full understanding of how FHBC is a risk for breast cancer is unclear. Therefore, the research is needed to further investigate the factors that trigger the development of breast cancer or increase MD in women with FHBC.

The aim of the present study was to examine the association between alcohol consumption and MD in Japanese women. We also assessed the joint risk of alcohol consumption and FHBC.

Participants and methods

Participants

This cross-sectional study was performed at the medical checkup unit of Ebina Health Service Center, Ebina, Japan. The study subjects included women who underwent routine health check-ups, including screening for breast cancer and metabolic syndrome between April 2012 and March 2013. Women 30–74 years old, within the age range for mammography screening, were included. We excluded 79 participants because of a previously diagnosed ($n=2$) or a newly diagnosed ($n=3$) breast cancer and those who had incomplete responses to the alcohol or reproductive questionnaires (n = 74). Eligible subjects included 477 premenopausal women and 308 postmenopausal women. Among the postmenopausal women, there were 14 women with a history of hormone replacement therapy (HRT) use. This study was approved by the Ebina Sougou Medical Center Institutional Review Board (approval number No. 287). Approval was based on the ethical guidelines of the Declaration of Helsinki.

Clinical data

Weight (kg), height (cm), and waist circumferences (cm) were measured at time of the mammography. From these measurements, the BMI (kg/m^2), an indicator of obesity, was calculated. A self-administered questionnaire was used to collect information about health behaviors and BC risk factors, specifically FHBC, number of live births, menopause status, and use of HRT.

Assessment of alcohol consumption

As a routine part of the general health check-up, all participants had already completed a simple self-administered lifestyle questionnaire, recording the average frequency of alcohol intake according to the following categories: almost never, 1–3 days per week, 4–6 days per week, and daily drinkers. We calculated the unit measurement of alcohol for the average weekly intake of each beverage on the basis of the known alcohol concentration. The average weekly alcohol consumption was calculated assuming that 180 ml (one unit) of Japanese sake, 630 ml (one bottle) of beer, 90 ml (one unit) of shochu or 2.5 glasses of wine contain 25 g of ethanol, as this is the typical ethanol content of Japanese sake, beer, and shochu. Weekly alcohol consumption was divided into three categories; less than 35 g per week (< 35 g/week), 35 to less than 140 g per week (35–140 g/week), and 140 g or more per week (≥ 140 g/week).

Mammographic density according to the breast imaging reporting and data system (BI-RADS)

Mammograms from the mediolateral oblique and craniocaudal view were obtained for each woman. They were taken using a Senographe DS, GE health care mammography machine. All the films were read by the same group of Ebina Sougou hospital Board-certified radiologists. The reader of the mammogram was blinded to other study data. MD was classified into low density (LD) and high density (HD) following the BI-RADS. LD was categorized as BI-RAD1, breast consisting almost entirely of fat, and BI-RAD2, scattered fibroglandular densities. HD was defined as BI-RAD3, heterogeneously dense breast tissue, and BI-RAD4, extremely dense breast tissue.

Statistical analysis

The student's unpaired *t* test was used to compare the averages of continuous variables and the Chi-square test was used to compare the proportions of categorical variables between LD and HD groups.

Unconditional logistic regression was performed to calculate the odds ratio (OR) and 95% confidence intervals (CI) for the categories of alcohol consumption with statistical significance set at 5%. The OR was adjusted for factors known to be associated with MD (age, BMI, parity and FHBC). Analyses were stratified according to menopausal status. In an additional logistic regression analysis, we assessed the joint effect of alcohol drinking and FHBC.

All statistical analyses were performed using SPSS software program (SPSS, Chicago, IL, USA).

Results

The mean age at mammography screening was 49.2 years and the mean BMI was 22.1 kg/m^2. Postmenopausal women accounted for 39% of the participants. Of these, 5.4% were past HRT users.

BI-RADS (1) almost entirely fat, (2) scattered fibroglandular densities, (3) heterogeneously dense, and (4) extremely dense represented 5%, 34%, 52% and 9% of the population, respectively (Fig. 1).

This cross-sectional study included 497 women with HD and 288 women with LD. The baseline characteristics of participants with HD and LD are summarized in Table 1. Compared with women with LD, women with HD had a lower BMI, fewer children, a larger proportion of premenopausal women, and were younger ($p < 0.001$). The two groups were comparable with respect to FHBC, HRT age at menarche, age at first birth and breast feeding.

The results of the adjusted logistic regression are presented in Tables 2, 3, 4 and 5.

When compared with alcohol abstainers, the overall analysis showed that women who consumed alcohol ≥ 140 g/week (highest alcohol consumption) had an increased risk of HD (OR 2.1, 95% CI 1.2–3.9 $p = 0.01$) after adjusting for age, parity, BMI and FHBC. The linear trend with increasing alcohol consumption was statistically significant ($p = 0.009$) (Table 2).

Within the group of premenopausal women, those with the highest alcohol consumption had an increased risk of HD (OR 2.3, 95% CI 1.0–5.3 $p = 0.05$) after adjusting for age, parity, BMI and FHBC. And the linear trend with increasing alcohol consumption was statistically significant ($p = 0.02$) (Table 3).

Similar results were observed among postmenopausal women. The OR among women with the highest alcohol consumption was 2.0 (95% CI 0.9–4.7 $p = 0.09$) after adjusting for age, parity, HRT, BMI and FHBC (Table 4). Table 5 shows the joint effect of alcohol consumption and FHBC. The joint risk of alcohol consumption and FHBC (OR 1.5, 95% CI 0.8–2.2) was lower than the sum of the

Table 1 Characteristics of the study population by LD or HD

Characteristic	Women with LD ($n = 288$)	Women with HD ($n = 497$)	p
Age, mean (SD)	52 (9.8)	47.4 (8.1)	0.001
BMI	23.8 (3.7)	21.2 (2.9)	< 0.001
Parity	1.8 (0.9)	1.4 (1.0)	< 0.001
Age at menarche*	12.1 (1.3)	12.2 (1.3)	0.3
Age at first birth**	28.0 (4.1)	28.3 (4.6)	0.5
Breast feeding (> 12 months)	50.2 (%)***	51.6	0.6
Menopausal status (%)			
Premenopausal	46.6	70.0	
Postmenopausal	53.4	30.0	< 0.001
HRT	2.4	1.4	0.6
FHBC	18	20	0.5
Relative degree			
1 58			
2 ≤ 89			

Missing data *21% **20% ***17%

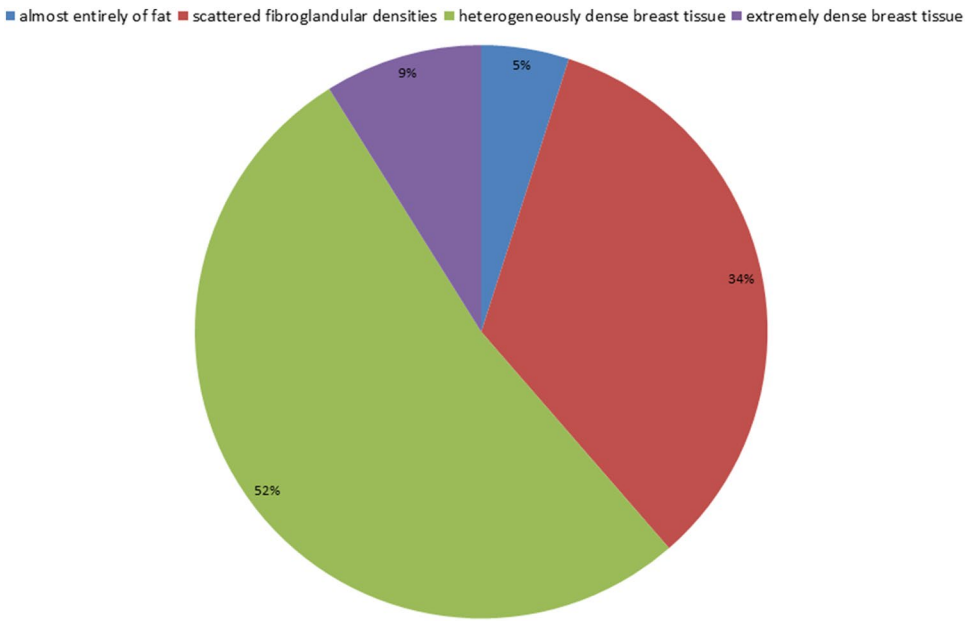

Fig. 1 Distribution of MD according to BI-RADS categories in all women

Table 2 Result of logistic regression for alcohol consumption and high MD(HD) in all women

Alcohol consumption (g/week)	HD	LD	Unadjusted OR (95% CI)	*p*	Adjusted[a] OR (95% CI)	*p*
0	262	191	Ref		Ref	
≦35	141	60	1.7 (1.2–2.4)	0.003	1.5 (1.0–2.3)	0.03
35<, <140	34	18	1.4 (0.8–2.5)	0.3	1.1 (0.6–2.1)	0.8
140≦	60	19	2.3 (1.3-4.0)	0.003	2.1 (1.2–3.9)	0.01
Trend test *p*				0.01		0.009

[a]Adjusted for age, BMI, parity, HRT and FHBC

Table 3 Result of logistic regression for alcohol consumption and high MD(HD) in premenopausal women

Alcohol consumption (g/week)	HD	LD	Unadjusted OR (95%CI)	*p*	Adjusted* OR (95%CI)	*p*
0	179	86	Ref		Ref	
≦35	100	29	1.7 (1.0–2.7)	0.04	1.5 (0.9–2.4)	0.2
35<, <140	24	11	1.0 (0.5–2.2)	0.9	1.0 (0.4–2.3)	0.9
140≦	40	8	2.4 (1.1–5.4)	0.03	2.3 (1.0-5.3)	0.05
Trend test *p*				0.03		0.02

*Adjusted for age, BMI, parity and FHBC

Table 4 Result of logistic regression for alcohol consumption and high MD(HD) in postmenopausal women

Alcohol consumption (g/week)	HD	LD	Unadjusted OR (95% CI)	*p*	Adjusted[a] OR (95% CI)	*p*
0	83	105	Ref		Ref	
≦35	41	31	1.7 (1.0–2.9)	0.07	1.7 (0.9–3.0)	0.09
35<, <140	10	7	1.8 (0.7–5.0)	0.3	1.2 (0.4–3.5)	n.s.
140≦	20	11	2.3 (1.0-5.1)	0.04	2.0 (0.9–4.7)	0.09
Trend test *p*				0.01		0.07

[a]Adjusted for age, BMI, parity and FHBC

Table 5 Joint risk between alcohol consumption and FHBC for HD

	LD (*n* = 288)	HD (*n* = 497)	OR (95% CI)[a]	*p*
Abstainer without FHBC	159	211	Ref	
Abstainer with FHBC	32	51	1.4 (0.8–2.3)	0.2
Drinker without FHBC	78	187	1.7 (1.2–2.5)	0.004
Drinker with FHBC	19	48	1.5 (0.8–2.8)	0.2

[a]Adjusted for age, BMI, parity and HRT

individual risks for alcohol consumption (OR 1.7, 95% CI 1.2–2.5) and FHBC (OR 1.4, 95% CI 0.8–2.3) (Table 5).

Discussion

A number of studies have shown that alcohol consumption plays multiple mechanistic roles in breast carcinogenesis, through hormone-dependent and hormone-independent pathways [17, 18]. As a hormone-dependent mechanism of action, alcohol consumption increases circulating estrogen level in both premenopausal and postmenopausal women, partly due to the aromatization of androgens to estrogens [18]. Cumulative lifetime exposure to estrogen plays an important role in the risk of breast cancer, and reports indicate that breast cancer is positively associated with estrogen exposure [19]. Several studies also suggest that alcohol can increase liver IGF-1 levels [20] and that

elevated IGF was reported to be associated with breast cancer risk [21]. MD refers to the extent of radiologically dense breast tissue, reflecting differences in breast tissue composition, and is a strong and independent predictor of breast cancer risk [1, 2].

One hypothesis to explain this biological mechanism is that increased endogenous sex hormones and IGF may increase epithelial cell proliferation in the breast and thereby increase MD [22]. Alcohol consumption may increase breast cancer risk by increasing MD.

A recent meta-analysis showed a positive association between alcohol intake and MD [23]. However, the studies included Caucasian women as the study subjects. Of note, Japanese women and Caucasian women differed on several crucial points.

First, Japanese women seem to have lower breast cancer rates compared with Western Countries [5]. Second, the peak ages differed between the two groups. The peak age for breast cancer was found to be between 40 and 50 years in Japan, whereas the peak age in Western countries was found to be between 60 and 70 years [24]. Third point, Japanese women have different physical proportions, including breast size and BMI. BMI is a strong predictor for MD and is inversely associated with MD [7]. A number of studies have suggested ethnic variations in MD [25, 26]. Asian women including Japanese women were reported to have a higher proportion of dense breasts than Caucasian women [25]. As would be expected, HD prevalence was higher in this study population than among Caucasian populations. This study of Japanese women confirmed a positive association between alcohol consumption and MD and is an important contribution to the literature since evaluations of MD in relation to breast cancer risk factors are limited.

FHBC and reproductive history are nonmodifiable risk factors for breast cancer. Postmenopausal obesity and alcohol consumption are well-established modifiable risk factors as the association between these risk factors and MD has been reported in many studies [6, 7]. Older age, parity, postmenopausal status, and high BMI were inversely associated with MD.

A number of epidemiological studies have evaluated whether the impact of alcohol intake on breast cancer risk may be modified by other risk factors, such as BMI and genetic differences [27, 28]. However, there are a few studies examining whether the association between alcohol consumption and MD is modified by other factors [29]. Evidence from Western countries indicates that the association between alcohol consumption and MD was modified by FHBC [29]. MD was positively associated with alcohol intake, and its association was significantly stronger in those with a FHBC [29]. Previous studies showed that women with FHBC were more likely to have higher MD. And that, MD and FHBC may be influenced by genetic overlap [30].

This study evaluated whether the impact of alcohol intake on MD is influenced by a FHBC in Japanese women. However, we found little evidence for the joint effect of alcohol consumption and FHBC. Since a small number of alcohol drinkers with FHBC were included in this population, further studies on the correlation between MD, alcohol consumption and FHBC may be necessary.

A dose–response relationship between alcohol consumption and breast cancer risk has been reported in many studies [27]. Similarly, studies have found that alcohol intake was dose-dependently associated with MD. A positive association was reported in Mediterranean populations with alcohol consumption levels of 84 g/week [31]. It has also been demonstrated that the breast cancer risk was significantly increased among Japanese women who consumed at least 100–150 g of alcohol per week [27]. Our results showed that the OR for HD was significantly increased among all women with the highest alcohol intake ($\geq$ 140 g/week of ethanol) compared with abstainers (OR 2.1, 95% CI 1.2–3.9 $p = 0.01$). The association between alcohol consumption and MD appears to be comparable to the dose-dependent association between alcohol consumption and breast cancer risk.

There are several potential limitations to our study. MD was visually evaluated using the BI-RADS classification. Recently, computer-assisted methods have been developed to calculate the percentage of MD and these measurements are more objective and quantifiable [32]. However, reports indicate that the visual assessment of MD, including BI-RADS evaluation, are highly reproducible when appropriate training is provided [33]. The evaluation of MD was performed by highly experienced radiologists as part of routine hospital practice. Our study design also avoided the opportunity for systematic errors as readings were performed without knowledge of the subject characteristics.

Further, we cannot exclude the possibility that our results were influenced by selection bias. The study subjects were selected from subjects undergoing breast cancer screening as part of routine health check-ups and these health-conscious women are less likely to consume a large amount of alcohol compared to the general population. The study population included women with low levels of alcohol intake, with 50% of the subjects being abstainers, while only 10% were in the highest alcohol consumption group. However, the Japanese National Health and Nutrition Survey reported that the percentage of women who consume alcohol has risen to the extent that the risk of lifestyle-related diseases is elevated in recent decades [34]. It is noteworthy that the positive association between MD and alcohol consumption was demonstrated despite the low alcohol intake in this population.

In conclusion, to the best of our knowledge, this is the first study evaluating the influence of alcohol consumption on MD among Japanese women. Multivariate analysis indicates that alcohol consumption is positively associated

with MD in Japanese women. Further studies are required to establish whether the effect of alcohol consumption on MD is modified by a FHBC.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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