Introduction

There is a variation in the incidence of breast cancer among countries [1]. Although Japan has a lower risk of breast cancer than Western countries, breast cancer ranks first in terms of the age-standardized rates of cancers among women as a whole, and its incidence continues to increase [1]. From the viewpoint of breast cancer risk, changes in exposure to reproductive and anthropometric risk factors among Japanese women [2, 3] may be responsible for this increase [4].

Among various risk factors for breast cancer, alcohol consumption has been considered important in Western countries. A meta-analysis including 53 studies showed that alcohol consumption was related to breast cancer risk [5]. In another meta-analysis including 98 studies, the combined odds ratio for drinkers versus non-drinkers was 1.22 (95% confidence interval (CI) 1.09–1.37) [6]. In addition, epidemiologic studies in Western countries have also demonstrated that the risk attributable to alcohol consumption might be modified by nutrient intake or exogenous female hormone use [7–9]. For example, breast cancer risk appeared to be increased among alcohol drinkers with a low intake of folate [8, 10].

On the other hand, in Japan, the association of alcohol consumption with breast cancer risk has been unclear. Two earlier cohort studies demonstrated no significant relationship between alcohol consumption and breast cancer risk [11, 12], whereas more recent cohort studies showed that higher alcohol consumption was associated with an increased risk of breast cancer [13, 14]. The available epidemiologic data regarding the association between alcohol drinking and breast cancer risk in Japan appear to be insufficient [15]. Japanese women may have different lifestyles from women in Western countries; for example, the proportion of exogenous female hormone users in Japan is lower than in Western countries [3] and the Japanese diet is rather unique [16]. Therefore, the risk associated with alcohol consumption confirmed in Western countries may not necessarily be applicable to Japanese women.

In the population-based cohort study, we evaluated the association of alcohol consumption with breast cancer risk among Japanese women, taking into account modifiable risk factors such as nutrient intake.

Materials and methods

Study cohort

This study was based on the Miyagi Cohort Study, whose study design has been described in detail elsewhere [17]. Briefly, 25,279 men and 26,642 women aged 40–64 years living in 14 municipalities, which were randomly selected from 62 municipalities in Miyagi Prefecture, Northeastern Japan, were entered into a cohort on June 1, 1990. A self-administered questionnaire on various health habits was delivered between June and August, 1990. Usable questionnaires were collected from 22,836 men and 24,769 women, and the response rates were 90.3 and 93.0%, respectively. All the residents in the study area were entered into the cohort, and the response rates of questionnaires were very high; thus, the subjects were thought to be sufficiently representative of this area.

In this study, 705 individuals who were diagnosed as having cancer before the baseline survey and 4,837 for whom information about alcohol drinking habits was lacking were excluded. Consequently, 19,227 women were entered into the analytic cohort. The study protocol was approved by the institutional review board of Tohoku University School of Medicine. This study was conducted in accordance with the principles of the Declaration of Helsinki. We considered the return of self-administered questionnaires signed by the subjects to imply their consent to participate in the study.

Questionnaire at the baseline survey

The questionnaire covered personal history including age, height, weight, education level, occupation, family history of breast cancer in mother or sisters, general lifestyle factors including cigarette smoking, walking status, and dietary history, menstrual and reproductive histories, and exogenous female hormone use. Dietary history including alcohol intake was 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 baseline 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 for these composition tables [18]. For the assessment of alcohol consumption, the questionnaire asked firstly if subjects were never, past, or current drinkers. Never drinkers were defined as women who had never or hardly ever drunk alcohol. Past drinkers were defined as those who had quit drinking before the baseline survey. Past or current drinkers were asked to state the age at which they had started drinking, frequency of drinking [almost every day (more than five times a week), three to four times a week, one to two times a week, and less than once a week (occasional)], the types of alcohol beverages consumed [Japanese *sake*, Japanese spirits (*shochu*), beer, whisky, wine and others], and the volume drunk on each occasion. The amount of alcohol consumed per day was calculated as: (total amount of alcohol drunk on each occasion) × (frequency of drinking)/7. The Spearman

correlation coefficient for comparison of the amount of alcohol consumed estimated from the FFQ with the amount estimated from 12 daily diet records kept over a 1-year period was 0.60 for women [19].

Ascertainment of cases and follow-up

The subjects were followed from the start of the study until December 31, 2003. The end point of our analysis was incidence of breast cancer defined as the topography code C50.0–C50.9 according to the International Classification of Disease for Oncology, Second Edition (ICD-O-2). The incidence of breast cancer was confirmed by the Miyagi Prefecture Cancer Registry, which is one of the oldest and most accurate population-based cancer registries in Japan [20, 21]. The relevant cases were abstracted from the medical records of the hospitals by a medical doctor or trained medical records reviewer, except for the cases reported to the registry from an institution. The percentage registered by death certificates only (DCO) for breast cancer was 2.5% for women during 1991–2003.

A follow-up Committee was established consisting of the Miyagi Cancer Society, the Divisions of Community Health of all 14 municipalities, the Department of Health and Welfare, Miyagi Prefectural Government, and the Division of Epidemiology, Tohoku University School of Medicine. The Committee periodically reviewed the Residential Registration Record of each municipality. This checkup identified subjects who had either died or emigrated during the observation period. Follow-up of subjects who had moved from the study municipalities was discontinued because the Committee could not review the Residential Registration Record from outside the study area. During the study period, 1,182 women (6.1%) were lost to follow-up.

Statistical analysis

The person-years of follow-up were counted for each of the subjects from the start of the study until the date of diagnosis of breast cancer, the date of emigration from the study area, the date of death, or the end of follow-up, whichever occurred first. The mean follow-up period was 12.8 years. The exposure variables analyzed in this study were alcohol drinking status (never/past/current), frequency of alcohol drinking (never/occasional/1–2 times per week/3–4 times per week/5–7 times per week), age upon starting to drink (never/<25 year/≥25 to <35 year/≥35 year), amount of alcohol consumed per occasion (never/<11.5 g/≥11.5 to <23.0 g/≥23 g), and amount of alcohol consumed per day (never/<5.0 g/≥5.0 to <15.0 g/≥15.0 g). All these exposures were determined at the baseline.

The Cox proportional-hazard regression model was used to estimate hazard ratios (HRs) and 95% CIs for the incidence of breast cancer according to category of exposure variable and to adjust for confounding variables [22]. Never drinkers served as a reference group. Linear trends were tested in the Cox model by treating each exposure category as a continuous variable. We considered the following variables to be potential confounders: age, education level, occupation, cigarette smoking, walking status, body mass index, use of exogenous female hormones, menstrual and reproductive factors, and family history of breast cancer in mother or sisters, which are all known, or possible, risk factors for breast cancer. In addition, intakes of fat and folate, which have been suspected to confound the effect of alcohol consumption on breast cancer risk [7, 14, 23], were controlled for. In the analysis, the intakes of these nutrients were adjusted for energy intake, and were categorized by quintile based on the distribution among the population. Missing values for confounders were treated as an additional variable category, and were included in the model.

Separate analyses were conducted after dividing the subjects into premenopausal and postmenopausal status. Stratification according to some selected potential factors, such as exogenous female hormone use (ever, never) and intake of fat and folate (higher or lower than the median intake per day), was also conducted to evaluate their modification effects on the study variables.

The results were regarded as significant if the two-sided P values were <0.05. All statistical analyses were performed using SAS software (version 9.2; SAS Institute, Cary, NC).

Results

The characteristics of the study subjects at the baseline are presented in Table 1. During 246,703 person-years of follow-up from 19,227 subjects, 241 breast cancer cases were documented. At the baseline, 13,461(70.0%), 772(4.0%) and 4,994(26.0%) of the subjects were never, past and current drinkers, respectively. Current drinkers were slightly younger and had a longer period of education. Past or current drinkers tended to smoke. There was no large difference in nutrient intake between never and current drinkers. Heavy drinkers (≥15.0 g/day) tended to have specific characteristics; they tended to be less educated, and about 40% were current smokers. Furthermore, even though they consumed a higher amount of energy, mean intakes of fat and folate were lower than those in other categories.

The HRs and 95% CIs for current alcohol drinking status among women overall are presented in Table 2.

Table 1 Characteristics of study population according to drinking habit at baseline

	Never drinkers	Past drinkers	Total	Current drinkers			
				Alcohol amount consumed per day			
				<5.0 g	≥5.0 to <15.0 g	≥15.0 g	Missing
Number of subjects (*n*)	13461	772	4994	2915	945	568	566
Age group (%)							
40–44	21.4	23.7	33.1	38.0	28.5	31.9	17.0
45–49	15.5	17.9	21.1	21.5	21.0	22.2	18.7
50–54	18.7	18.0	17.9	17.0	18.9	18.5	20.0
55–59	21.9	22.0	15.5	13.6	17.1	15.1	23.0
60–64	22.5	18.4	12.3	9.8	14.5	12.3	21.4
Age (mean, years)	52.4 ± 7.4	51.7 ± 7.4	49.5 ± 7.2	48.6 ± 7.0	50.3 ± 7.2	49.6 ± 7.0	52.6 ± 7.2
Body mass index (%)							
<20	9.5	11.3	9.1	8.6	10.7	10.2	7.4
≥20 to <23	32.4	30.1	34.7	35.0	36.1	35.4	30.4
≥23 to <25	24.2	22.7	24.4	25.7	22.2	22.9	23.1
≥25	30.0	30.4	27.7	28.0	26.3	27.5	29.0
Missing	3.9	5.6	4.1	2.7	4.7	4.0	10.1
Smoking (%)							
Current smoker	3.9	25.6	15.8	10.7	18.3	40.1	13.1
Past smoker	0.9	10.1	2.9	2.5	3.4	5.1	2.1
Never smoker	86.4	49.7	63.8	73.2	62.6	43.1	37.8
Missing	8.9	14.5	17.5	13.5	15.7	11.6	47.0
Occuption (%)							
Housewife/no occupation	15.6	13.9	13.9	14.4	15.3	13.7	9.2
Others	68.8	65.0	70.4	72.8	71.0	72.4	55.7
Missing	15.6	21.1	15.7	12.9	13.7	13.9	35.2
Walking status (%)							
Longer than 1 h per day	42.1	38.5	39.7	39.9	40.4	37.9	39.2
Less than 1 h per day	51.0	53.9	52.8	55.2	53.3	54.8	37.3
Missing	6.8	7.6	7.5	4.9	6.2	7.4	23.5
Family history of breast cancer in mother or sisters (%)							
No	98.4	97.8	98.3	98.3	98.0	98.2	98.8
Yes	1.6	2.2	1.7	1.7	2.0	1.8	1.2
Educational level (%)							
Junior high school or less	37.2	39.1	32.9	31.1	32.3	36.6	39.8
High school	44.4	41.2	46.5	49.2	45.5	44.5	36.4
College/university or higher	12.4	10.0	13.9	15.0	15.6	11.6	8.1
Missing	6.1	9.7	6.6	4.7	6.7	7.2	15.7
Age at menarche (years) (%)							
≤13	22.3	25.5	27.8	31.3	27.0	26.1	12.7
14	21.7	20.7	23.6	25.6	22.6	21.8	16.4
15	20.2	16.3	18.6	19.0	18.4	19.5	16.3
≥16	23.9	23.3	19.4	17.3	21.8	22.0	24.0
Missing	11.8	14.1	10.6	6.8	10.2	10.6	30.6

Table 1 continued

	Never drinkers	Past drinkers	Total	Current drinkers			
				Alcohol amount consumed per day			
				<5.0 g	≥5.0 to <15.0 g	≥15.0 g	Missing
Parity number (%)							
0	2.4	4.5	2.9	2.8	3.4	4.0	1.4
1	6.8	10.6	7.3	7.0	8.5	8.5	6.4
2	39.6	34.5	40.2	42.1	40.0	40.3	30.2
3	32.5	26.2	31.3	32.9	29.9	28.0	28.6
4	9.8	10.8	9.1	8.7	8.8	8.8	11.7
5≤	3.4	5.3	3.2	2.7	3.6	3.2	4.8
Missing	5.5	8.2	6.1	3.8	5.8	7.2	17.0
Use of exogenous female hormones and/or OC (%)							
Never	75.9	69.6	71.8	74.3	72.5	70.6	58.7
Ever	10.2	14.0	14.8	15.4	15.1	15.8	9.7
Missing	13.9	16.5	13.5	10.3	12.4	13.6	31.6
Nutrient intake							
Energy (Kcal)	1325.9 ± 348.8	1268.1 ± 385.0	1312.1 ± 371.3	1334.9 ± 349.0	1289.9 ± 380.0	1372.8 ± 382.9	1170.9 ± 418.2
Fat intake (mean, g/day)	25.1 ± 9.1	24.3 ± 10.1	25.1 ± 9.5	26.1 ± 8.9	25.6 ± 9.5	21.3 ± 8.6	22.8 ± 11.8
Folate intake (mean, μg/day)	229.8 ± 89.0	221.9 ± 99.3	225.3 ± 91.8	229.9 ± 87.5	233.5 ± 92.0	210.9 ± 86.3	202.4 ± 11.5

Table 2 Hazard ratio (HR) and 95% confidence interval (CIs) of breast cancer incidence according to history of alcohol drinking

	Number of subjects	Cases	Person-years	Age-adjusted model		Multivariate-adjusted model 1[a]		Multivariate-adjusted model 2[b]	
				HR	95% CI	HR	95% CI	HR	95% CI
Never	13,461	171	173,506	1.00	(reference)	1.00	(reference)	1.00	(reference)
Past	772	4	9,601	0.42	0.16–1.13	0.39	0.14–1.08	0.39	0.14–1.07
Current	4,994	66	63,596	1.01	0.76–1.34	1.00	0.74–1.35	1.00	0.74–1.34

[a] Adjusted for age (continuous variable), body mass index (<20, ≥20 to <23, ≥23 to <25, ≥25), smoking (current, past, never), occupation (housewife/no occupation, others), walking (less than 1 h per day, longer than 1 h per day), educational level (junior high school or less, high school, college/university or higher), age at menarche (≤13, 14, 15, >16), parity number (0, 1, 2, 3, 4, ≥5), family history of breast cancer (present, absent), age at menopause (premenopausal, <48, 48–50, >50 years, missing for age at menopause, missing for menopausal status) and use of exogenous female hormones and/or OC (never, ever)

[b] Additionally adjusted for energy-adjusted intakes of fat (quintiles) and folate (quintiles) and energy intake

After adjustment for age, the HR and 95% CI for past drinkers was less than unity, 0.42 (0.16–1.13), but not statistically significant. The HR and 95% CI for current drinkers was 1.01 (0.76-1.34). After adjustment for potential risk factors for breast cancer in multivariate-adjusted model 1, the HRs and 95% CIs for past and current drinkers were 0.39 (0.14–1.08) and 1.00 (0.74–1.35), respectively. Further adjustment for intakes of fat and folate in multivariate adjusted model 2 showed quite similar results. In terms of menopausal status, the HRs and 95% CIs for breast cancer risk among current drinkers compared with never drinkers was 1.05 (0.70–1.56) for premenopausal women and 1.06 (0.66–1.71) for postmenopausal women (data not shown).

Table 3 shows the associations with breast cancer incidence according to frequency of drinking, age upon starting to drink, and amount of alcohol drunk per occasion and per day. After adjustment for potential risk factors for breast cancer in multivariate-adjusted model 1, women who were current frequent drinkers at 5–7 times per week appeared to have a decreased risk (HR = 0.66, 95% CI: 0.29–1.53). However, the trend test showed non-significance (P for trend = 0.94). The multivariate-adjusted model 2 taking into account nutritional factors also showed no association (P for trend = 0.89). Early exposure to alcohol drinking at age under 25 had no significant relationship to breast cancer risk (HR in multivariate-adjusted model 2 = 0.91, 95% CI: 0.57–1.44). A higher amount of alcohol consumed

Table 3 Hazard ratio (HR) and 95% confidence interval (CIs) of breast cancer incidence according to frequency, first age, and amount of alcohol drinking

	Number of subjects	Cases	Person-years	Age-adjusted model			Multivariate-adjusted model 1[a]			Multivariate-adjusted model 2[b]		
				HR	95% CI	*P* for trend	HR	95% CI	*P* for trend	HR	95% CI	*P* for trend
Alcohol drinking frequency[c]												
Never	13,461	171	173,506	1.00	(reference)	0.95	1.00	(reference)	0.94	1.00	(reference)	0.89
Current	2,031	26	26,142	0.95	0.63–1.44		0.94	0.62–1.44		0.94	0.61–1.43	
Occasional												
1–2 per week	1,205	19	15,353	1.21	0.75–1.95		1.23	0.76–1.99		1.22	0.76–1.98	
3–4 per week	779	12	9,807	1.21	0.67–2.17		1.18	0.65–2.14		1.17	0.64–2.12	
5–7 per week	666	6	8,265	0.72	0.32–1.62		0.66	0.29–1.53		0.65	0.28–1.49	
		234										
Alcohol drinking—age upon starting to drink[c]												
Never	13,461	171	173,506	1.00	(reference)	0.81	1.00	(reference)	0.94	1.00	(reference)	0.93
Current												
<25	1,824	23	23,074	0.92	0.59–1.45		0.92	0.58–1.46		0.91	0.57–1.44	
25–35	1,366	19	17,340	1.06	0.66–1.71		1.05	0.65–1.70		1.05	0.64–1.70	
>35	1,174	13	15,059	0.90	0.51–1.58		0.96	0.54–1.70		0.96	0.54–1.70	
Alcohol drinking—amount per occasion[c]												
Never	13,461	171	173,506	1.00	(reference)	0.77	1.00	(reference)	0.93	1.00	(reference)	0.98
Current												
<11.5 g	2,685	40	34,457	1.13	0.80–1.60		1.14	0.80–1.62		1.14	0.80–1.62	
≥11.5 to <23.0 g	1,298	17	16,512	1.00	0.61–1.65		0.98	0.59–1.63		0.97	0.58–1.62	
≥23.0 g	604	8	7,454	1.04	0.51–2.11		0.95	0.46–1.99		0.93	0.44–1.94	
Alcohol drinking—amount per day[c]												
Never	13,461	171	173,506	1.00	(reference)	0.64	1.00	(reference)	0.80	1.00	(reference)	0.85
Current												
<5.0 g	2,915	40	37,494	1.03	0.73–1.46		1.03	0.72–1.47		1.02	0.72–1.46	
≥5.0 to <15.0 g	945	15	11,917	1.24	0.73–2.11		1.21	0.71–2.07		1.21	0.71–2.08	
≥15.0 g	568	7	6,972	0.98	0.46–2.10		0.90	0.41–1.98		0.87	0.40–1.91	

[a] Adjusted for age (continuous variable), body mass index (<20, 20≤ <23, 23≤ <25, 25≤), smoking (current, past, never), occupation (housewife/no occupation, others), walking (less than 1 h per day, longer than 1 h per day), educational level (junior high school or less, high school, college/university or higher), age at menarche (≤13, 14, 15, 16<), parity number (0, 1, 2, 3, 4, 5≤), family history of breast cancer (present, absent), age at menopause (premenopausal, <48, 48-50, >50 years, missing for age at menopause, missing for menopausal status) and use of exogenous female hormones and/or OC (never, ever)

[b] Additionally adjusted for energy-adjusted intakes of fat (quintiles) and folate (quintiles) and energy intake

[c] Women of past drinkers were excluded from the analysis

per occasion (≥23 g/occasion) also had no statistically significant relationship to breast cancer risk (HR in multivariate-adjusted model 2 = 0.93, 95% CI: 0.44–1.94). Regarding the risk for the amount of alcohol consumed per day, women who consumed ≥5.0 to <15.0 g/day tended to have an increased risk (HR in multivariate-adjusted model 2 = 1.21, 95% CI: 0.71–2.08); however, no such increased risk was observed among women who consumed ≥15.0 g/day (HR in multivariate-adjusted model 2 = 0.87, 95% CI: 0.40–1.91). The trend test showed no linear relationship between the amount of alcohol consumed per day and breast cancer risk (*P* for trend = 0.85).

Table 4 shows the results of analyses stratified according to exogenous female hormone use and fat and folate intake. Among users of female hormone, higher alcohol intake (≥15.0 g/day) was associated with an increased risk of breast cancer, but not to a statistically significant degree. Analysis according to folate intake indicated that the association between alcohol intake and breast cancer risk differed between women with low and high intakes of folate. Among women with low folate intake, HRs tended to increase with increasing alcohol consumption (*P* for trend = 0.09); however, no such trend was observed among women with high folate intake. The interaction term

Table 4 Hazard ratio (HR) and 95% confidence interval (CIs) of breast cancer incidence according to history of alcohol drinking within strata of potential risk factors

	Use of exogenous hormones[a]						Fat intake[b]						Folate intake[c]					
	Ever			Never			<24.5 g/day[d]			≥24.5 g/day			<219 μg/day[d]			≥219 μg/day		
	Cases	HR	95% CI	Cases	HR	95% CI	Cases	HR	95% CI	Cases	HR	95% CI	Cases	HR	95% CI	Cases	HR	95% CI
Alcohol drinking																		
Never	17	1.00	(reference)	131	1.00	(reference)	86	1.00	(reference)	85	1.00	(reference)	81	1.00	(reference)	90	1.00	(reference)
Past	1	1.09	0.12–9.57	2	0.27	0.07–1.11	3	0.58	0.18–1.89	1	0.20	0.03–1.48	3	0.57	0.18–1.83	1	0.22	0.03–1.60
Current	5	0.66	0.22–1.97	55	1.10	0.79–1.54	33	1.06	0.69–1.62	33	0.96	0.63–1.47	40	1.29	0.86–1.93	26	0.77	0.49–1.22
Alcohol drinking—amount per day[e]																		
Never	17	1.00	(reference)	131	1.00	(reference)	86	1.00	(reference)	85	1.00	(reference)	81	1.00	(reference)	90	1.00	(reference)
Current																		
<5.0 g/day	2	0.39	0.08–1.88	32	1.05	0.70–1.56	21	1.20	0.74–1.97	19	0.88	0.53–1.47	22	1.27	0.78–2.08	18	0.85	0.50–1.43
≥5.0 to <15.0 g/day	2	1.54	0.32–7.45	13	1.37	0.77–2.45	6	1.12	0.48–2.60	9	1.32	0.65–2.68	9	1.68	0.83–3.40	6	0.88	0.38–2.04
≥15.0 g/day	1	1.67	0.17–16.73	6	0.98	0.42–2.32	4	0.86	0.30–2.46	3	1.09	0.33–3.56	6	1.58	0.65–3.86	1	0.28	0.04–2.03
P for trend	0.86			0.55			0.45			0.76			0.09			0.21		
	Interaction $P = 0.42$						Interaction $P = 0.55$						Interaction $P = 0.09$					

[a] Adjusted for age (continuous variable), body mass index (<20, ≥20 to <23, ≥23 to <25, ≥25), smoking (current, past, never), occupation (housewife/no occupation, others), walking (less than 1 h per day, longer than 1 h per day), educational level (junior high school or less, high school, college/university or higher), age at menarche (≤13, 14, 15, >16), parity number (0, 1, 2, 3, 4, ≥5), family history of breast cancer (present, absent), age at menopause (premenopausal, <48, 48–50, >50 years, missing for age at menopause, missing for menopausal status), energy-adjusted intakes of fat (quintiles) and folate (quintiles) and energy intake

[b] Adjusted for age (continuous variable), body mass index (<20, ≥20 to <23, ≥23 to <25, ≥25), smoking (current, past, never), occupation (housewife/no occupation, others), walking (less than 1 h per day, longer than 1 h per day), educational level (junior high school or less, high school, college/university or higher), age at menarche (≤13, 14, 15, >16), parity number (0, 1, 2, 3, 4, ≥5), family history of breast cancer (present, absent), age at menopause (premenopausal, <48, 48–50, >50 years, missing for age at menopause, missing for menopausal status), use of exogenous female hormones (never, ever), and energy-adjusted intakes of folate (quintiles)

[c] Adjusted for age (continuous variable), body mass index (<20, ≥20 to <23, ≥23 to <25, ≥25), smoking (current, past, never), occupation (housewife/no occupation, others), walking (less than 1 h per day, longer than 1 h per day), educational level (junior high school or less, high school, college/university or higher), age at menarche (≤13, 14, 15, >16), parity number (0, 1, 2, 3, 4, ≥5), family history of breast cancer (present, absent), age at menopause (premenopausal, <48, 48–50, >50 years, missing for age at menopause, missing for menopausal status), use of exogenous female hormones (never, ever), and energy-adjusted intakes of fat (quintiles)

[d] Median value of energy-adjusted intake per day

[e] Women of past drinkers were excluded from the analysis

(folate intake * amount of alcohol consumed per day) was marginally significant ($P = 0.09$). Regarding to fat intake, breast cancer risk for alcohol intake did not differ between women with low and high intake ($P = 0.55$).

Discussion

This population-based prospective cohort study in Japan revealed that breast cancer risk was not associated with alcohol drinking history, age upon starting to drink, frequency of drinking, or the amount of alcohol consumed per occasion or per day. Analysis according to menopausal status also yielded similar results. Our result is important because few studies in Asian countries have evaluated the relationship between alcohol drinking and breast cancer risk in a prospective setting [5, 6].

Alcohol consumption has been considered a convincing risk factor for breast cancer in Western countries. In Japan, two cohort studies have demonstrated positive associations between current alcohol consumption of more than 15 g/day [13] or 150 g/week (21.4 g/day) [14] and breast cancer risk. However, our study did not support such a significant association for alcohol consumption. Although women with a current alcohol intake of ≥5.0 to <15.0 g/day tended to have an increased risk of breast cancer, the risk was lower for women who consumed ≥15 g/day. We interpreted the inconsistency between our study and others as follows. First, Japanese women probably have lifestyle factors that differ from those of women in Western countries. For example, the higher prevalence of hormone replacement therapy (HRT) in Western countries may contribute to the significant relationship. In previous studies, the significant risk elevation resulting from alcohol consumption was limited to women receiving HRT [7]. Our study also observed an increased risk among exogenous female hormone users, although this was non-significant (Table 4). However, the prevalence of hormone use in our cohort was much lower than that in Western countries [2]. Therefore, alcohol intake might have no overall relationship with breast cancer risk. Second, differences in distributions of exposure and confounding variables among study areas may affect the risk. Our study was conducted in a confined area, whereas the major population-based cohort studies in Japan have covered multiple areas [14]. The associations with alcohol consumption might therefore have been confounded by some area-related factors. For example, heavy drinkers (≥15.0 g alcohol/day) in our cohort included high proportions of current smokers and individuals with a shorter period of education (Table 1), unlike subjects in other studies. This inconsistency may reflect the background characteristics of heavy drinkers in different study areas [24].

The presence of unmeasured mechanisms could also have explained our results. One such mechanism is gene polymorphism. Acetaldehyde is a metabolite of ethanol that causes genetic damage [23], and is metabolized by aldehyde dehydrogenases (ALDHs). The inactive form of ALDH resulting from gene polymorphism is rare in Caucasians, but frequent in Japanese [25, 26], and this is thought to cause accumulation of acetaldehyde, and thus increase the incidence of cancer. However, previous studies have shown that this polymorphism is not related to breast cancer risk in Japanese [27]. The polymorphisms of ALDH among Japanese may not have much influence on the alcohol–breast cancer risk relationship in a practical situation.

Several studies have suggested that the association of alcohol consumption with breast cancer risk might be modified by dietary factors [8, 10]. In our study, the amount of alcohol consumed per day was positively associated with breast cancer risk among women with low folate intake, although statistical analysis demonstrated marginal significance. This finding suggests that alcohol drinkers with low folate intake may have a higher risk of breast cancer, even though overall breast cancer risk for alcohol drinkers is close to unity. Alcohol acts as antagonist for folate; therefore, low folate intake is thought to increase breast cancer risk among alcohol drinkers through impaired DNA repair [28].

Analysis based on history of alcohol drinking showed that past drinkers tended to have a lower risk of breast cancer. No association was observed for age upon starting to drink or frequency of drinking. Previous cohort studies have revealed that age upon starting to drink [13, 29] and frequency of drinking [13] were not related to breast cancer risk, although the risk for past drinkers was unity. To elucidate the associations between drinking patterns and breast cancer risk, further studies are required.

The strengths of this study included its prospective design and the high quality of the follow-up survey. Participants were recruited from the general population, and breast cancer cases were identified by the Miyagi Prefecture Cancer Registry, which is one of the most accurate of its kind in Japan. Furthermore, the rate of loss to follow-up was low. Therefore, several types of bias, i.e., selection and information bias, were avoided. Another strength was that we controlled for nutrient intake, such as that of fat and folate. Only one previous study in Japan has controlled for these factors [14]. With regard to limitations, we must consider the effects of missing data. Subjects for whom details of alcohol drinking status were unknown were excluded. HR and 95% CI for these subjects was 0.73 (0.53–1.03) compared to never drinkers. This exclusion was unlikely to have distorted the results.

In summary, this prospective cohort study has demonstrated no associations of alcohol drinking status,

frequency of alcohol drinking, amount of alcohol consumed on one occasion or per day, and age upon starting to drink with breast cancer risk among Japanese women. In our analysis, stratified according to use of female hormone, higher alcohol intake was associated with an increased risk among hormone users, but this was not statistically significant. In relation to folate intake, the amount of alcohol consumed per day was marginally associated with breast cancer risk among women with low folate intake. These findings suggest that alcohol intake has no overall impact on breast cancer risk, and that the nutritional factors such as folate intake may modify the alcohol–breast cancer risk relationship. Further studies are required to clarify the association of alcohol intake with breast cancer risk among Japanese women.

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Randomized Controlled Trial on Effectiveness of Ultrasonography Screening for Breast Cancer in Women Aged 40–49 (J-START): Research Design

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In cancer screening, it is essential to undertake effective screening with appropriate methodology, which should be supported by evidence of a reduced mortality rate. At present, mammography is the only method for breast cancer screening with such evidence. However, mammography does not achieve sufficient accuracy in breasts with high density at ages below 50. Although ultrasonography achieves better accuracy in Breast Cancer detection even in dense breasts, the effectiveness has not been verified. We have planned a randomized controlled trial to assess the effectiveness of ultrasonography in women aged 40–49, with a design to study 50 000 women with mammography and ultrasonography (intervention group), and 50 000 controls with mammography only (control group). The participants are scheduled to take second round screening with the same modality 2 years on. The primary endpoints are sensitivity and specificity, and the secondary endpoint is the rate of advanced breast cancers.

Key words: breast cancer screening – mammography – ultrasonography – randomized controlled trial

INTRODUCTION

Breast cancer is one of the most common cancers worldwide (1). The age-standardized incidence rate is the first among all female cancers, and it is continuously increasing in Japan (2,3), although Japan has a lower risk of breast cancer in comparison with Western countries. The incidence peaks at ages 45–49, and the mortality peaks at ages 55–59 in Japan (2). In breast cancer screening, it is essential to undertake effective screening with appropriate methodology. Effective screening should be supported by evidence of a reduced mortality rate. At present, mammography (MG) is the only method for breast cancer screening that has such evidence. However, MG does not achieve sufficient screening accuracy in breasts with high mammary gland density. Dense breasts are common at ages below 50 and are more common in Japanese populations than in Western populations (4). As the US Preventive Services Task Force (USPSTF) recommends against routine screen MG in women aged 40–49 years, the issue of breast imaging to screen women aged 40–49 still remains unclear (5).

Since ultrasonography (US) achieves better accuracy in breast cancer detection even in dense breasts (6) and supplemental screening US has the potential to depict early breast cancers not seen on MG (6–8), several single-institution observational studies in screening setting began. As mentioned in the WHO guidelines, 'population-based cancer screening' conducted as a public health program should be undertaken only when there is evidence of a

reduced mortality rate (9). Before introducing any new technology in population-based breast cancer screening, it is essential to evaluate the effectiveness. However, randomized controlled trials (RCTs), cohort studies or case–control studies have not been completed to assess the efficacy of screening US to reduce breast cancer mortality, and the effectiveness has not been verified.

Therefore, we have planned an RCT to assess effectiveness of screening US for breast cancer, the Japan Strategic Anti-cancer Randomized Trial (J-START) in 2006. The defined study population is women aged 40–49 years, because this is the age range at which breast cancer peaks in Japan (2) and because a high percentage of Japanese women aged 40s have dense breast. This is a large-scale controlled trial, designed to study 50 000 women with MG and US (intervention group) and 50 000 controls with MG only (control group).

The primary endpoints of this trial are the inter-group comparisons of the sensitivity and specificity, and the secondary endpoint is the inter-group comparison of the accumulated incidence rate of advanced breast cancer during the follow-up period. The most important index in the evaluation of the effectiveness of cancer screening is the mortality rate from the cancer in question in the target population. However, in view of the natural history of breast cancer, the 4-year period scheduled in the strategic study grant is too short to observe a significant inter-group difference. Although the rate of advanced breast cancer could be a surrogate for mortality reduction, it is necessary to have a system that has the long-term follow-up of the survival status of individuals even after the completion of the strategic study, J-START.

This study may have several limitations. First, the screening interval is 2 years, despite evidence that screening MG at age 40–49 years is more effective with annual screening. The recent USPSTF, however, recommends biannual MG screening in view of reducing 'harm', i.e. higher recall rate at age 40–49 years (5). Secondly, the study population, which is so different from that in Western countries, may limit the generalization of study outcomes. Most countries in Asia, however, demonstrate the similar trend of breast cancer incidence as observed in Japan; therefore, this trial may influence their health strategy against breast cancer. Nevertheless, for women aged 40–49 years even in Western countries, there is a limitation of MG screening as the USPSTF recommends against the routine use of screening MG for this age group. Thirdly, the study may be underpowered to provide follow-up data on breast cancer deaths because of the low breast cancer risk of native Japanese women. In this context, as much as 100 000 women are targeted in this trial to ensure the statistical power be sufficient enough in comparison between the two groups.

PROTOCOL DIGEST OF THE STUDY

Purpose

The aim of this study is to assess the effectiveness of screening US for breast cancer in women aged 40–49 (Fig. 1).

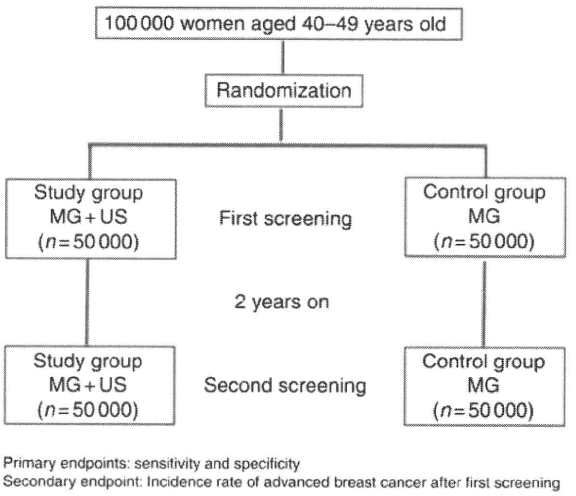

Figure 1. J-START study design. MG, mammography; US, ultrasonography.

Study Setting

This study is a multi-institutional prospective RCT, with 42 participating centers in 23 prefectures in Japan as of 31 March 2011.

Endpoints

The primary endpoints of this trial are sensitivity and specificity, based on the data of each incremental cancer detection rate, false-positives and false-negatives should be forthcoming in 2 years. The secondary endpoint is the rate of advanced breast cancers, as this has been demonstrated in the screening MG RCTs to be a surrogate for mortality reduction (10).

Eligibility Criteria

Inclusion criteria are as follows:

(i) women aged 40–49 years when registered;
(ii) women signed the informed consent to participate in the study.

Exclusion criteria are as follows:

(i) women with a history of breast cancer;
(ii) women with a history of malignant disease other than breast cancer within 5 years;
(iii) women in severe condition, who are not expected to live for 5 years.

Treatment Methods

Patient Assignments

Each participating center confirms the participants' eligibility and screening methods are assigned according to the random

number provided by the Japan Clinical Research Supporting Unit (J-CRSU) Data Center. Cluster randomization is also used in some institutions.

Screening Method and Assessment

For the intervention arm, US and MG are performed at the same time. For the control arm, MG is performed. The technologists and the physicians involved in this trial are asked to finish 2-day, 16-h education program for the standardization of US screening for breast cancer. Regarding the procedure in screening with US, the handheld US is performed by a technologist or by a physician, and later, the US image is interpreted by a physician. An interpretation of MG is performed by a physician who is not regulated to be the same doctor interpreting US image or not, although the categorization of the two modalities are defined separately in the protocol. The findings of MG and/or US are subsequently evaluated by authorized screeners and are classified into five categories as follows: Category 1, negative; Category 2, benign finding(s); Category 3, probably benign finding(s); Category 4, suspicious abnormality; and Category 5, malignancy. The women who are rated in Category 3 or higher by the MG and/or US are referred for further diagnostic examinations.

Statistical Analysis

The sample size was calculated on the hypothesis that adjunct US is expected to improve sensitivity of the intervention group compared with the control group. Our previous data demonstrated the lower sensitivity of MG screening, 71% in women aged 40–49, when compared with those in women aged 50–59 and 60–69, 85 and 86%, respectively (11). Assuming that the sensitivity increases from 71 to 86% by adding US to MG, 42 500 subjects for each arm is needed to make it 5% statistical significance (two-sided) with 80% power. Thus, the number of 100 000 subjects (two arms combined) is set to be a targeted sample size to verify the primary endpoint, a sensitivity improvement in the intervention group when compared with the control group.

Follow-up Period

The participants are invited to be screened 2 years after the first recruitment or asked to answer questionnaires of health status, history of receiving other screening program, incidence of breast cancer, and history of hospital consultation with any breast symptoms within 2 years. For evaluating the actual evidence of a reduced mortality rate of the intervention group compared with the control group, there must be needed to establish follow-up strategies for a long time period and systematic, nationwide population-based cancer registries.

Registration of the Protocol

The J-START was registered on the University Hospital Medical Information Network Clinical Trial Registration (UMIN-CTR), Japan (registration number: UMIN000000757), on 2007. Details are available at the following address: https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr.cgi?function=brows&action=brows&type=summary&recptno=R000000910&language=E.

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Conflict of interest statement

None declared.

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Classifying Breast Masses in Volumetric Whole Breast Ultrasound Data: A 2.5-Dimensional Approach

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Abstract. The aim of this paper is to investigate a 2.5-dimensional approach in classifying masses as benign or malignant in volumetric anisotropic voxel whole breast ultrasound data. In this paper, the term 2.5-dimensional refers to the use of a series of 2-dimensional images. While mammography is very effective in breast cancer screening in general, it is less sensitivity in detecting breast cancer in younger women or women with dense breasts. Breast ultrasonography does not have the same limitation and is a valuable adjunct in breast cancer detection. We have previously reported on the clinical value of volumetric data collected from a prototype whole breast ultrasound scanner. The current study focuses on a new 2.5-dimensional approach in analyzing the volumetric whole breast ultrasound data for mass classification. Sixty-three mass lesions were studied. Of them 33 were malignant and 30 benign. Features based on compactness, orientation, shape, depth-to-width ratio, homogeneity and posterior echo were measured. Linear discriminant analysis and receiver operating characteristic (ROC) analysis were employed for classification and performance evaluation. The area under the ROC curve (AUC) was 0.91 using all breast masses for training and testing and 0.87 using the leave-one-mass-out cross-validation method. Clinically significance of the results will be evaluated using a larger dataset from multi-clinics.

Keywords: ultrasound breast mass, classification, geometric feature, echo feature.

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1 Introduction

Mammography is very effective in breast cancer detection. It is the routine technique used in breast cancer screening in women who have no symptom of breast cancer. However, mammography is less sensitivity in detecting breast cancer in younger women or women with dense breasts. This is due to the inherited limitations of x-ray employed in the image acquisition in mammography. Breast ultrasonography is another long-standing technique in breast imaging and is a valuable adjunct in breast cancer detection. Distinguished from mammography, the technique employs acoustic waves and does not have the same limitation as mammography. However, it is not without its shortcomings.

Currently, ultrasound breast examination is routinely performed by an ultrasonographer or ultrasonologist. A small hand-held probe of size about 4 cm is used and the ultraonographer/ ultrasonologist runs the probe over the entire breast or pre-identified regions during an examination. The technique can provide very valuable information in the hands of experienced examiners but is in general time consuming. Results are operator independent and reproducibility is poor. A novel breast scanning system that can acquire the data of the entire breast quickly, systematically and repeatedly with precision will be of great advantage.

We have previously introduced a prototype whole breast ultrasound scanner for auto-acquisition of volumetric breast ultrasound data [1]. Diagnostic value of the data was investigated [2]. The volumetric ultrasound data of a whole breast consist of a stack of two-dimensional images, each depicting an axial slice image of the breast. In exploiting the benefit of volumetric data, three-dimensional analysis was used in our previous study in classifying malignant and benign breast masses [3].

One issue noted in our previous three-dimensional analysis was that the data was anisotropic. Anisotropic data are generally computationally cumbersome. One of the common practices would be to resample the data to create isotropic voxel. However, this would not be a good practice for our volumetric whole breast data as the resolution in one direction (z-direction, normal to the axial plane) is about 8 to 10 times lower than that in the other two directions. The discrepancy is large and a reliable model for interpolation cannot be guaranteed. Another option is to increase the number of data points in the z-direction in the raw data. This could be achieved by reducing the interval between adjacent slice images. Options for slice intervals are 2 mm, 1 mm and 0.5 mm. Corresponding unilateral breast study contains 84, 168 and 336 (axial) images, respectively, with acquisition time increases from 20, to 40 and 80 seconds, respectively. The increase in number of axial unnecessarily burdens the interpreters while longer acquisition time leads to problems such as image blurring due to patient movement. Neither of the above options is desirable in this situation as the first one relied on interpolated slice images of which accuracy of the image details to be employed in the computer-aided image analysis cannot be guaranteed. The second one imposes on a clinical practice to collect extra data which is a burden to the practice at no clear clinical benefits. After taken the above into consideration, this paper investigates the efficacy of a 2.5-dimensional analysis, a step between 2-dimensional and 3-dimensional analyses.

2 Method

2.1 Ultrasound Data

Volumetric full-breast ultrasound data were used in this study. The data included 63 breast masses. Of them 33 were malignant and 30 (16 cysts; 14 fibroadenomas) were benign. The malignant and benign masses were related to 29 and 24 breasts, respectively. All the masses were annotated by a radiologist experienced in breast ultrasound and the malignant masses were proven by biopsy. With the patient in prone position, a diagnostic ultrasound system Prosound-II SSD-5500 (Aloka Co., Ltd, Japan) and a prototype full-breast scanner ASU-1004 (Aloka Co., Ltd, Japan) (Figure 1) were used to acquire the full-breast images. The scanner ASU-1004 was equipped with a 5-10 MHz 6 cm linear probe. Operating in a fixed pattern, the probe scanned an area of 16 × 16 cm^2 in 3 sweeps, covering the full-field of a breast. The original scan images were B-mode breast section images in DICOM format with an overlap margin of 1 cm on each of the 'stitching' side. Volumetric full-breast data were generated by 'stitching' corresponding images in the 3 sweeps together (Figure 2). Details of the scanner can be found in [4-6].

The full-breast ultrasound scans were performed in the period 2003-2004 at the Center of Optical Medicine, Dokkyo University School of Medicine, Tochigi, Japan where a prototype full-breast scanner ASU-1004 was located. The size of each (stitched) B-mode image in the constructed volumetric full-breast data was 694 × 400 pixels with a spatial resolution of 0.23 mm/pixel and a slice-to-slice interval of 2 mm.

The images had a gray scale resolution of 8 bits. For each mass, a series of axial slice images containing that mass is employed in the 2.5-dimensional analysis (Figure 3). Features are measured individually on each slice image. The same feature measured on difference slice images are combined at a later stage.

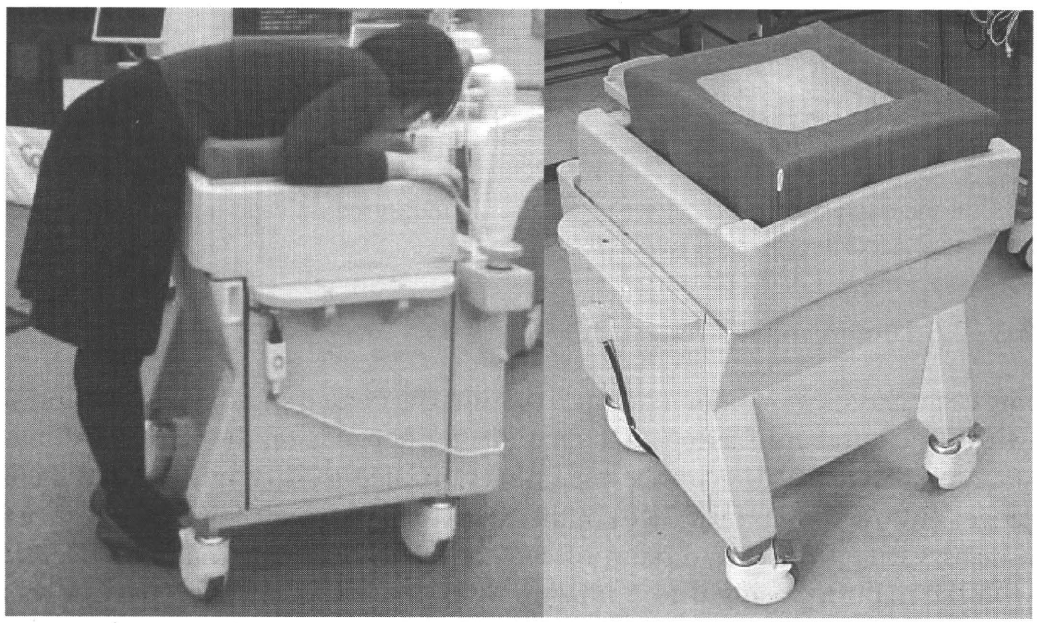

Fig. 1. The prototype full-breast scanner ASU-1004 (right) with a patient in prone position (left)

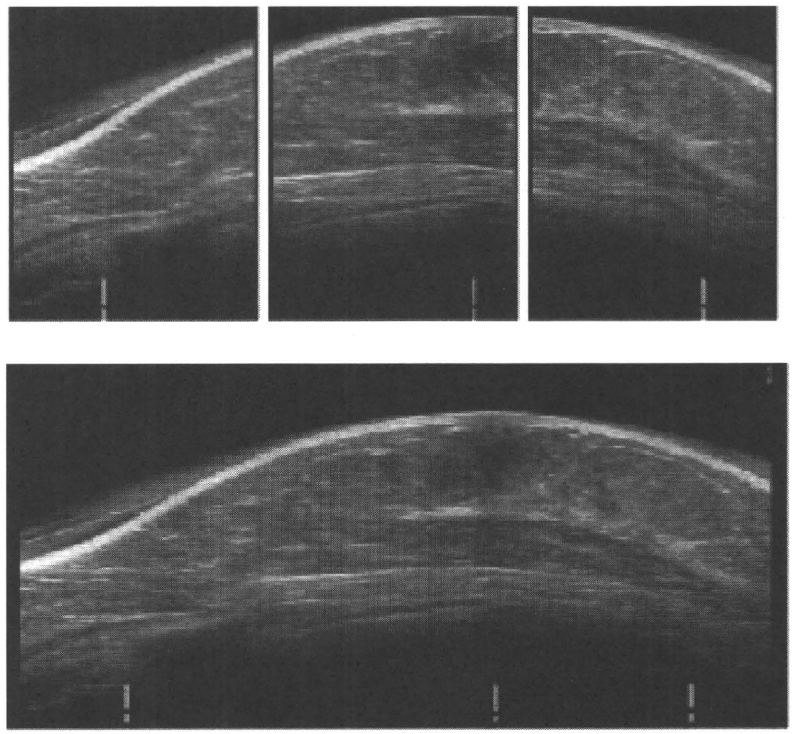

Fig. 2. Corresponding breast section slice images in the 3 sweeps (above) are 'stitched' together to form a slice image in the volumetric full-breast data (below)

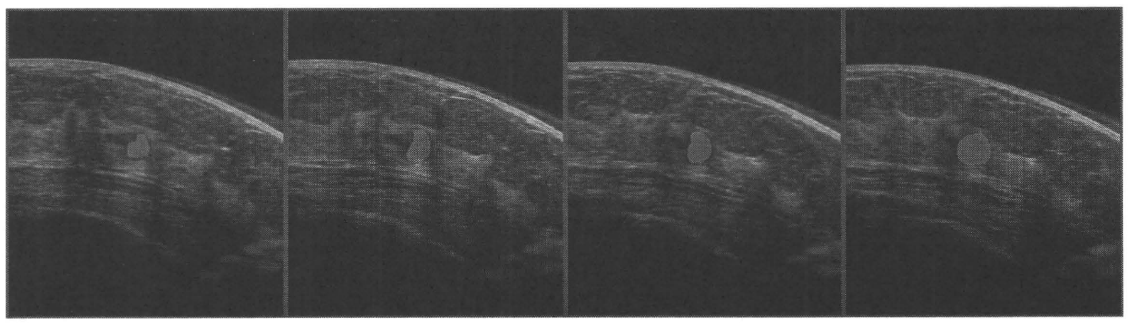

Fig. 3. 2.5-dimensional analysis. In this example, a series of 4 images containing the mass were used in the analysis. The same set of features is measured on each images and is combined at a later stage according to a set rule.

2.2 2.5-Dimensional Analysis

For each mass lesion, a number of axial images containing the mass lesion were identified. The number of associated slice images depends on the size of the mass and the slice-to-slice interval. With the use of a 2 mm slice-to-slice interval and the lesion size ranges from 5 mm to over 3 cm in this study, the number of associated slice image for a mass varies from a minimum of 1 to 2 images to a maximum of over 10 images, with the majority being 4 to 6 images. With the series of slice images containing the mass lesion identified, lesion boundaries were delineated manually and lesions in each of the slice images were segmented.

After the segmentation process, features were measured on the lesions depicted in each of the slice images. Six features were defined. They were compactness, orientation, shape, depth-to-width ratio, homogeneity and posterior analysis. These six features were similar to the features selected in our previous study [3] and were based on the image features that radiologists' found useful and routinely consulted in breast ultrasound images interpretations. A summary of the six features is given in the next paragraph.

In general, compactness (C) measures the degree of roundness of an object and is given by

$$C = 4 \times \pi \times A / S^2 \tag{1}$$

where A and S are the area and circumference of the object, respectively. Benign masses are usually round in shape while malignant masses are more likely to be irregular or oval in shape. Orientation measures the angle (in degrees) between the horizontal axis and the major axis of the ellipse that has the same second-moments as the object and is given by

$$\tan^2 \theta + \frac{M(2,0) - M(0,2)}{M(1,1)} = 0 \tag{2}$$

where $M(p, q)$ is the pq^{th}-order moment and is given by

$$M(p,q) = \sum_{i,j} i^p j^q .$$

Depth-to-width (DW) ratio is another feature that can provide information of the orientation of an (elongated) object. This feature can be simply defined as the ratio of the height to the width of the smallest bounding box containing the mass. Homogeneity of the mass is computed using the variance of the intensity inside a mass. Benign masses such as cysts generally display homogeneity (small variance) inside the mass. Posterior echo is also another feature to distinguish benign and malignant lesions. The absence of posterior echo is an indicator of malignant lesion.

The above six features were measured on the lesions in each individual slice images. In other words, the six features were repeatedly measured on a series of mass cross-sectional images separated at a fixed interval of 2 mm.

The 2.5-dimensional analysis is based on features measured in a series of 2-dimensional images. For each breast mass, measurements of the same feature measured on a series of images are combined according to a rule which is feature-specific. For example, the depth-to-width (D/W) ratio measures the depth (vertical extent) of a mass to the width (horizontal extent) of a mass in a 2-dimensional image. Malignant lesions are more rigid and less compressible when subject to external force, hence the D/W ratio of malignant lesions is generally high. On the other hand, benign lesions such as cysts, which are usually filled with fluid or lipids, are more compressible and deformable. Hence, their D/W ratios are generally low. In other words, higher the D/W ratio, more likely is the lesion malignant. So in a 2.5-dimensional analysis, the maximum of the D/W ratios measured on a series of 2-dimensional images of a lesion is the strongest evidence for malignancy. Table 1 listed the rules in combining the multi-slice measurements of the same feature towards 2.5-dimensional analysis assuming strongest evidence for malignancy.

Table 1. Rules for combining multi-slice feature measurements in 2.5-dimensional analysis

FEATURES	*2.5-DIMENSIONAL ANALYSIS*
Compactness	minimum
Orientation	maximum
Depth-to-width ratio	maximum
Posterior echo	minimum
homogeneity	maximum
Shape	maximum

3 Results

Linear discriminant analysis and receiver operating characteristic (ROC) analysis were employed for classification and performance evaluation. Discriminative powers of the six 2.5-dimensional features (combined over slice images) were analyzed in Table 2. The discriminative power of individual feature was indicated by the area under the ROC curve (AUC) obtained when using that feature alone in classifying the mass as benign or malignant. Both the resubstitution AUC using all breast masses for training and testing and the leave-one-mass-out cross-validation AUC are depicted. Table 2 shows that among the six features, three of them have strong discriminative power, namely, orientation, depth-to-width ratio and posterior echo.

When using all the six features for classification, the area under the ROC curve (AUC) was found to be 0.91 using all breast masses for training and testing (resubstitution) and 0.87 using the leave-one-mass-out cross-validation method.

Among a number of classifiers, linear discriminant analysis was chosen for its robustness. Its hyperplane decision surface makes it less susceptible for over-training which is preferable for studies with small samples.

Table 2. Discriminative powers of the six features indicated by the area under the ROC curve (AUC)

FEATURES	*AUC (resubstitution)*	*AUC (leave-one-mass-out)*
Compactness	0.64	0.64
Orientation	0.82	0.79
Depth-to-width ratio	0.83	0.84
Posterior echo	0.84	0.84
homogeneity	0.66	0.50
Shape	0.60	0.58

4 Discussion and Conclusion

The classification based on 2.5-dimensional analysis in this study resulted in high accuracy in discriminating malignant and benign lesions in volumetric breast ultrasound data

with anisotropic voxel. AUC indices in this study are in general high and similar to that based on 3-dimensional analysis in our previous study [2]. However, direct comparisons cannot be made. This is because the sample sizes in the two studies were different (63 masses in this study and 36 in the previous 3-d study) and shape feature was introduced in the current 2.5-dimensional analysis but not in the previous 3-dimensional study. In addition, though features definitions are very similar in the two studies, different algorithms were used to compute the features in the two studies. Slight variations in the interpretation of individual features may exist.

Plan for further work in this project is two-folded. (1) a larger database is required to confirm the results in this study. (2) Classification categories will also be extended to include normal breast tissue lumps and other artifacts in the breast which are the false positives found in the detection stage.

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Adiposity, adult weight change and breast cancer risk in postmenopausal Japanese women: the Miyagi Cohort Study

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BACKGROUND: The role of adult weight change in breast cancer (BC) risk is unclear in Japanese women.

METHODS: A total of 10 106 postmenopausal women aged 40–64 years (the Miyagi Cohort) were followed from 1990 to 2003, and 108 BC cases were identified. Hazard ratios (HRs) were estimated according to body mass index (BMI) at the current age and at the of age 20 years, and weight change since age 20 years.

RESULTS: Higher current BMI was associated with an increased risk of BC (P for trend = 0.02), whereas higher BMI at the age 20 years was inversely associated with this risk (P for trend = 0.002). There was a significant association between weight change since age 20 years and BC risk (P for trend = 0.0086). Compared with stable weight, HR was 0.35 for weight loss of 5 kg or more (P for weight loss trend = 0.04) and 1.55 for weight gain of 12 kg or more (P for weight gain trend = 0.05).

CONCLUSION: Adiposity at younger and current age has differential effects on BC risk among postmenopausal women; weight gain in adulthood being associated with an increased, and weight loss with a decreased risk.

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The incidence of breast cancer (BC) shows variations among countries and although Japan has a lower risk of BC than Western countries, its age-standardised incidence is the highest among female cancers, and it is increasing (Matsuda *et al*, 2008). The increase of BC incidence may be attributed to a change in the proportion of women in the population who have reproductive and anthropometric risk factors (Minami *et al*, 2004). Among such risk factors, the associations between adiposity and BC risk have been extensively investigated, mainly in the Western countries (Lahmann *et al*, 2004; Morimoto *et al*, 2002; Reeves *et al*, 2007). In relation to adiposity, weight gain has also been associated with an increased risk of postmenopausal BC in several prospective studies (Ahn *et al*, 2007; Barnes-Josiah *et al*, 1995; Eliassen *et al*, 2006; Feigelson *et al*, 2004; Lahmann *et al*, 2005). In Japan, however, few prospective studies have evaluated the association with adiposity (Iwasaki *et al*, 2007; Kuriyama *et al*, 2005). Also, data are sparse regarding the effect of body weight change (Hirose *et al*, 1999; Kyogoku *et al*, 1990).

We therefore conducted a population-based cohort study, in which we evaluated the association of adiposity in different periods, that is, at current age and at age 20 years, with BC risk and examined the change in risk resulting from body weight gain and loss since the age of 20 years among postmenopausal Japanese women.

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MATERIALS AND METHODS

Our analysis used the Miyagi Cohort Study, whose design has been described in detail elsewhere (Fukao *et al*, 1995; Kawai *et al*, 2010). Briefly, 25 279 men and 26 642 women aged 40–64 years living in 14 municipalities, selected randomly from among the 62 municipalities in Miyagi Prefecture, Northeastern Japan, were entered into a cohort on 1 June 1990. A self-administered questionnaire on various health aspects was delivered to these subjects between June and August 1990. Usable questionnaires were returned by 22 836 men (90.3%) and 24 769 women (93.0%). After excluding men, women with a history of cancer ($n = 705$), who were premenopausal ($n = 9131$), with undefined menopausal status ($n = 642$) and for whom data on menopausal status were missing ($n = 2927$), 11 364 postmenopausal women remained (Kawai *et al*, 2010). After further excluding women with missing data or extreme values for current height or current weight or weight at age 20 years ($n = 1258$), 10 106 postmenopausal women contributed to this study. The study protocol was approved by the institutional review board of Tohoku University School of Medicine. We considered the return of self-administered questionnaires signed by the subjects to imply their consent to participate in the study.

The questionnaire covered personal history including current height (centimeters) and weight (kilograms) and weight at age 20 years and details of general lifestyle including menstrual and reproductive histories. The self-reported current height and weight data were highly correlated with measured data (correlation coefficient: 0.82 for height and 0.97 for weight) in a subsample of postmenopausal women ($n = 2921$), although we were unable to validate the data for weight at age 20 years.

As a measure of adiposity, body mass index (BMI) was used. The BMI at the current age and at age 20 years, calculated as weight divided by the square of current height ($kg\,m^{-2}$), respectively. To analyze BC risk for adiposity in the different periods, the study women were categorised using quartile points of BMI at age 20 years, respectively: <20.5, $\geqslant 20.5-<22.0$, $\geqslant 22.0-<23.8$ and $\geqslant 23.8$. Subjects with a current BMI of 23.8 and higher were further divided into two groups on the basis of median value in the range between 23.8 and the largest current BMI, as the BMI at the current age was skewed towards a higher value than at age 20 years. Finally, women were categorised as follows: current BMI <20.5, $\geqslant 20.5-<22.0$, $\geqslant 22.0-<23.8$, $\geqslant 23.8-<25.9$ and $\geqslant 25.9$; BMI at age 20 <20.5, $\geqslant 20.5-<22.0$, $\geqslant 22.0-<23.8$ and $\geqslant 23.8$. Weight change from age 20 years to the current age was calculated as the difference between current weight and weight at age 20. Subjects were also categorised into seven groups as follows: weight loss of $\leqslant -5$ and >-5 to $\leqslant -2$, stable weight of >-2 to $<+2$, and weight gain of $\geqslant +2$ to $<+5$, $\geqslant +5$ to $<+8$, $\geqslant +8$ to $<+12$ and $\geqslant +12$. The categorisation of weight loss was based on the median value, and that of weight gain was determined using quintile values.

Women were followed from the start of the study (1 June 1990) until 31 December 2003. The end point of our analysis was BC defined as the topography codes C50.0–C50.9 according to the International Classification of Disease for Oncology, Second Edition, and confirmed by the Miyagi Prefecture Cancer Registry, one of the oldest and most accurate population-based in Japan (Curado *et al*, 2007). In this registry, the percentage registered by death certificates only for BC was 2.5% during 1991–2003. A follow-up committee was also established, consisting of the Miyagi Cancer Society, the Divisions of Community Health of all 14 municipalities, the Department of Health and Welfare, Miyagi Prefectural Government, and the Division of Epidemiology, Tohoku University School of Medicine. The committee periodically reviewed the residential registration record of each municipality. During the study period, 491 women (4.9%) were lost to follow-up because of emigration.

Statistical analysis

The person-years of follow-up were counted for each of the subjects from the start of the study (1 June 1990) until the date of diagnosis of BC, the date of emigration from the study area, the date of death, or the end of follow-up (31 December 2003), whichever occurred first. The mean follow-up period was 12.8 years. The Cox proportional-hazard regression model was used to estimate BC hazard ratios (HRs) and 95% confidence intervals (CIs) according to category of exposure variable, that is, BMI at the current age, BMI at age 20 years and weight change from age 20 years to the current age, and to adjust for confounding variables (Cox, 1972). Linear trends, which were tested using the Cox model by treating each exposure category as a continuous variable, were regarded as significant if P-values were <0.05. We considered the following variables as potential confounders: age, education level, cigarette smoking, alcohol drinking, and time spent walking, which are known or suspected risk factors for BC. Menstrual and reproductive factors, exogenous female hormone use, and history of BC in the mother or sisters, some of which had been established as risk factors in our previous study (Kawai *et al*, 2010), were also considered to be adjusted for each other. In the analysis of weight change, height and weight at age 20 years were further adjusted for (Eliassen *et al*, 2006). Missing values for confounders were treated as an additional variable category, and were included in the model. To evaluate any independent effect of BMI during the different periods, analysis adjusting for both BMIs each other was also conducted. All statistical analyses were performed using the SAS software package (version 9.1; SAS Institute, Cary, NC ,USA).

RESULTS

The characteristics of the study subjects are presented in Tables 1 and 2. The subjects with a higher current BMI were less likely to smoke, whereas the subjects with a higher BMI at age 20 years tended to be older and to have a shorter period of education (Table 1). A total of 64.8% of the subjects had gained more than 2 kg since age 20 years (Table 2). The subjects who lost weight were heavier at age 20 years.

During 129 891 person-years of follow-up, 108 BC cases were documented. Table 3 shows the HRs and 95% CIs according to current BMI and BMI at age 20 years. After adjustment for confounding variables, current BMI was marginally associated with an increased BC risk (P for trend in multivariate-adjusted model 1 = 0.07). The BMI at age 20 years was inversely associated risk (P for trend in multivariate-adjusted model 1 = 0.01). Postmenopausal women with a BMI of $\geqslant 23.8$ at age 20 years showed half the risk (multivariate-adjusted HR = 0.44, 95% CI: 0.24–0.81) of women with a BMI of <20.5. Multivariate analysis adjusting for both BMIs each other demonstrated a stronger inverse association for BMI at age 20 years (P for trend in multivariate-adjusted model 2 = 0.002). The association of current BMI with risk was statistically significant (P for trend = 0.02).

Weight change since the age of age 20 years was significantly associated with the risk (multivariate-adjusted P for trend = 0.0086) (Table 4). Compared with women whose weight had been stable (lost or gained <2.0 kg), those who lost 5 kg or more were at a lower risk (multivariate-adjusted HR 0.35, 95% CI: 0.11–1.10). Women with a weight gain of 12 kg or more appeared to have a higher risk (HR 1.55, 95% CI: 0.70–3.45). According to weight loss and gain, weight loss was associated with a decreased risk (P for weight loss trend = 0.04), and weight gain with an increased risk (P for weight gain trend = 0.05). Although the data are not shown in the table, stratified analysis by the BMI at age 20 years revealed a clearer inverse association with weight loss among women who were heavier at age 20 years (BMI at age 20 years $\geqslant 23.8$; P for weight loss trend = 0.01).

DISCUSSION

In this population-based cohort study, we found associations between adulthood adiposity and weight change and BC risk among postmenopausal women. Risk differed for BMI between that at current age and that at age 20 years. Weight change from age 20 to current age was significantly associated with risk. These results provide some insight into the significance of adiposity and weight change in terms of BC risk in postmenopausal Japanese women.

This study found a positive association of current BMI with postmenopausal BC risk consistent with previous prospective studies (Iwasaki *et al*, 2007; Kuriyama *et al*, 2005; Lahmann *et al*, 2004; Morimoto *et al*, 2002; Reeves *et al*, 2007), and the fact that postmenopausal obese women have more oestrogens than lean women (Potischman *et al*, 1996), has a central role in BC aetiology. After menopause, oestrogen is synthesised mainly by aromatase in adipose tissue (Bulun *et al*, 2005). Another mechanism is that obese women may be in a state of hyperinsulinemia, insulin being a growth factor for BC cells. Insulin-like growth factor I may also affect risk among heavier women (Muti *et al*, 2002). On the other