Table 1 Characteristics of the study cohort

	BMI < 21.2	≥ 21.2 to< 23.3	≥ 23.3 to< 25.8	≥ 25.8	Total
Age (years) mean ± S.D.	53.7 ± 13.4	55.2 ± 11.2	58.9 ± 12.0	60.0 ± 11.9	57.0 ± 12.4
Person-years	963.0	1052.4	1020.1	997.3	4032.8
Patients (n)	163	166	161	163	653
All-cause death (n)	42	27	29	38	136
Breast cancer-specific death (n)	34	21	26	27	108
Smoking (%)					
Never	72.4	78.9	85.7	82.2	79.8
Current or Past	25.2	17.5	12.4	14.1	17.3
Missing	2.5	3.6	1.9	3.7	2.9
Stage (%)					
In situ or Locarized	39.9	43.4	34.2	39.3	39.2
Lymph node Metastasis	30.7	34.9	41.6	35.6	35.7
Local Invasion	10.4	6.6	9.9	8.0	8.7
Distant Metastasis	1.8	2.4	5.0	3.1	3.1
Missing	17.2	12.7	9.3	14.1	13.3
Hormone receptor (%)					
ER + or PgR+	58.9	57.8	65.2	69.3	62.8
ER-/PgR-	28.2	30.1	25.5	22.7	26.6
Missing	12.9	12.0	9.3	8.0	10.6
Radiation therapy (%)					
No	77.3	78.3	86.3	83.4	81.3
Yes	22.7	21.7	13.7	16.6	18.7
Chemotherapy (%)					
No	74.8	76.5	75.2	78.5	76.3
Yes	25.2	23.5	24.8	21.5	23.7
Endocrine therapy (%)					
No	75.5	75.9	79.5	71.2	75.5
Yes	24.5	24.1	20.5	28.8	24.5
No	95.1	92.8	90.7	86.5	91.3
Yes	4.9	7.2	9.3	13.5	8.7
Menopausal status (%) [a]					
Premenopausal	54.6	44.0	39.1	31.9	42.4
Postmenopausal	41.1	51.8	57.8	66.3	54.2
Missing		4.2	3.1	1.8	3.4
Physical activity (%)					
Almost no	51.5	53.0	45.3	46.6	49.2
More than one hour per week	43.6	39.8	46.0	50.3	44.9
Missing	4.9	7.2	8.7	3.1	6.0
Comorbidities (%) [b]					
No	86.5	80.1	71.4	67.5	76.4
Yes	13.5	19.9	28.6	32.5	23.6

[a] Menopause was defined as the cessation of menstrual periods due to natural or other reasons including surgery.
[b] Includes hypertension/ischemic heart disease/stroke/diabetes mellitus.
During a median follow-up period of 5.85 years, 136 all-cause and 108 breast cancer-specific deaths were observed.

Table 2 HR (95%CI) of all-cause death associated with BMI overall and by menopausal status

	BMI	Patients	Person-years	All-cause death	Age-adjusted HR	95% CI	Multivariate-adjusted HR	95% CI
All								
	<21.2	163	963.0	42	1.73	1.07 - 2.80	1.60	0.97 - 2.63
	≥21.2 to <23.3	166	1052.4	27	1.00 (reference)		1.00 (reference) [a]	
	≥23.3 to <25.8	161	1020.1	29	1.03	0.61 - 1.75	0.88	0.51 - 1.51
	≥25.8	163	997.3	38	1.37	0.83 - 2.25	1.46	0.87 - 2.44
p for trend						0.35		0.59
p for trend in women with BMI ≥21.2						0.18		0.11
Premenopausal								
	<21.2	89	556.1	18	2.04	0.88 - 4.69	1.75	0.71 - 4.29
	≥21.2 to <23.3	73	510.2	8	1.00 (reference)		1.00 (reference) [b]	
	≥23.3 to <25.8	63	391.6	11	1.74	0.70 - 4.35	1.61	0.63 - 4.11
	≥25.8	52	319.8	13	2.49	1.03 - 6.03	2.61	1.01 - 6.78
p for trend						0.52		0.29
p for trend in women with BMI ≥21.2						0.05		0.059
Postmenopausal								
	<21.2	67	371.6	20	1.56	0.82 - 2.98	0.93	0.47 - 1.86
	≥21.2 to <23.3	86	500.7	17	1.00 (reference)		1.00 (reference) [b]	
	≥23.3 to <25.8	93	589.2	16	0.74	0.37 - 1.47	0.45	0.21 - 0.94
	≥25.8	108	670.7	22	0.93	0.49 - 1.75	0.72	0.36 - 1.45
p for trend						0.086		0.2
p for trend in women with BMI ≥21.2						0.91		0.71
Pre v Post p for heterogeneity of trends						0.13		0.24
Pre v Post p for heterogeneity of trends in women with BMI ≥21.2						0.09		0.11

[a] Adjusted by age, stage (in situ or localized, lymph node metastasis, local invasion, distant metastasis, missing), hormone receptor (ER + or PgR+, ER-/PgR-, missing), radiation therapy (no, yes), chemotherapy (no, yes), endocrine therapy (no, yes), smoking (current, past, never, missing), family history of breast cancer in father, mother, brother or sister (no, yes), menopausal status (premenopausal, postmenopausal, missing), physical activity (almost no, more than one hour per week, missing) and comorbidities (no, yes).

[b] Adjusted by age, stage, hormone receptor, radiation therapy, chemotherapy, endocrine therapy, smoking, family history of breast cancer in father, mother, brother or sister, physical activity and comorbidities.

An increased risk of all-cause death was found among premenopausal women with BMI ≥25.8 kg/m^2. Trend test for premenopausal women with BMI ≥21.2 kg/m^2 also showed a marginal dose–response relationship.

ER/PR status (Table 4). Among women with ER + or PgR + tumors, BMI was significantly associated with both all-cause (multivariate-adjusted p for trend = 0.02) and breast cancer-specific death (multivariate-adjusted p for trend = 0.031) if the women had a BMI of ≥21.2 kg/m^2. Heavier women (≥25.8 kg/m^2) with ER + or PgR + tumors showed a higher risk of breast cancer-specific death (4.95, 1.05–23.35). BMI <21.2 kg/m^2 carried a higher risk of all-cause (2.91, 1.09–7.77) and breast cancer-specific death (7.23, 1.57–33.34) compared to women with BMI ≥21.2 to <23.3 kg/m^2. No significant association between BMI and all-cause and breast cancer-specific death was found for ER-/PgR- tumors. For all-cause and breast cancer-specific death, the trends were not significantly different between ER + or PgR + and ER-/PgR- women with BMI ≥21.2 kg/m^2 (P for heterogeneity of trends = 0.10 and 0.13, respectively).

Discussion

This study demonstrated that higher BMI was significantly associated with all-cause death among premenopausal patients after adjustment for clinical and known factors that are associated with the mortality risk of breast cancer patients. Analysis stratified according to hormonal receptor status showed that higher and lower BMI were associated with increased risks of all-cause and breast cancer-specific death only for patients with ER + or PgR + tumors. Previous studies that investigated the relationship between BMI and outcome in Japanese breast cancer patients considered only a few known risk factors as covariates, included only a small number of cases, and did not assess hormone receptor status [25,26]. Our study is of importance in having assessed the relationship between BMI and all-cause or breast cancer-specific death by taking into account multiple risk

Table 3 HR (95%CI) of breast cancer-specific death associated with BMI overall and by menopausal status

BMI	Patients	Person-years	Breast cancer-specific death	Age-adjusted HR	95% CI		Multivariate-adjusted HR	95% CI	
All									
<21.2	163	963.0	34	1.69	0.98 - 2.92		1.59	0.90 - 2.81	
≥21.2 to <23.3	166	1052.4	21	1.00 (reference)			1.00 (reference) [a]		
≥23.3 to <25.8	161	1020.1	26	1.32	0.74 - 2.35		1.20	0.66 - 2.17	
≥25.8	163	997.3	27	1.40	0.79 - 2.49		1.46	0.81 - 2.64	
p for trend						0.64			0.87
p for trend in women with BMI ≥21.2						0.20			0.18
Premenopausal									
<21.2	89	556.1	15	1.60	0.68 - 3.80		1.22	0.47 - 3.14	
≥21.2 to <23.3	73	510.2	8	1.00 (reference)			1.00 (reference) [b]		
≥23.3 to <25.8	63	391.6	11	1.77	0.71 - 4.41		1.62	0.63 - 4.20	
≥25.8	52	319.8	10	1.95	0.77 - 4.96		1.68	0.61 - 4.65	
p for trend						0.48			0.34
p for trend in women with BMI ≥21.2						0.18			0.51
Postmenopausal									
<21.2	67	371.6	15	1.89	0.87 - 4.11		1.22	0.52 - 2.86	
≥21.2 to <23.3	86	500.7	11	1.00 (reference)			1.00 (reference) [b]		
≥23.3 to <25.8	93	589.2	13	1.09	0.49 - 2.45		0.79	0.32 - 1.93	
≥25.8	108	670.7	14	1.02	0.46 - 2.26		1.03	0.43 - 2.50	
p for trend						0.15			0.56
p for trend in women with BMI ≥21.2						0.86			0.45
Pre v Post p for heterogeneity of trends						0.13			0.27
Pre v Post p for heterogeneity of trends in women with BMI ≥21.2						0.29			0.80

[a] Adjusted by age, stage (in situ or localized, lymph node metastasis, local invasion, distant metastasis, missing), hormone receptor (ER + or PgR+, ER-/PgR-, Missing), radiation therapy (no, yes), chemotherapy (no, yes), endocrine therapy (no, yes), smoking (current, past, never, missing), family history of breast cancer in father, mother, brother or sister (no, yes), menopausal status (premenopausal, postmenopausal, missing), physical activity (almost no, more than one hour per week, missing) and comorbidities (no, yes).

[b] Adjusted by age, stage, hormone receptor, radiation therapy, chemotherapy, endocrine therapy, smoking, family history of breast cancer in father, mother, brother or sister, physical activity and comorbidities.

No dose–response relationship between BMI and breast cancer-specific death was found.

factors for breast cancer, in addition to menopausal status and hormone receptor status, in Japanese women.

Our results demonstrated that higher BMI was significantly associated with all-cause death among premenopausal patients, and were consistent with several previous observational studies of premenopausal or younger women that demonstrated poorer overall survival with increased BMI [2,4,17,18,20]. A meta-analysis including 43 studies showed that the effect of obesity on higher all-cause or breast cancer-specific death was larger among premenopausal than among postmenopausal women [21]. Our present results demonstrated that the effect of higher BMI was greater for all-cause death than for breast cancer-specific death (HR = 2.61; 95% CI: 1.01–6.78 for BMI ≥25.8 kg/m^2 for all-cause death; HR = 1.68; 95% CI: 0.61–4.65 for BMI ≥25.8 kg/m^2 for breast cancer-specific death). One possibility is that women with higher BMI have poorer overall survival because of a higher risk of comorbidities. Therefore, we reanalyzed the data after excluding patients who had comorbidities. Within the limited statistical power, the effect of higher BMI was significant for all-cause death among premenopausal patients (HR = 3.42; 95% CI: 1.23–9.47 for BMI ≥25.8 kg/m^2 for all-cause death, p for trend for BMI ≥21.2 kg/m^2 = 0.0068) and not significant for breast cancer-specific death. These were perhaps potential mediators of the adverse effect of higher BMI in premenopausal breast cancer patients, independent of comorbidities.

In the present study, an association of higher BMI with poorer outcome was seen in women with ER + or PgR + tumors. This result is consistent with previous studies that have indicated an association of higher BMI with poorer outcome, being especially pronounced among

Table 4 HR (95%CI) of all-cause and breast cancer-specific death associated with BMI by hormone receptor status

	BMI	Patients	Person-years	All-cause death Number of death	HR [a]	95% CI	Breast cancer-specific death Number of death	HR [a]	95% CI
ER + or PgR+									
	<21.2	96	581.5	18	2.91	1.09 - 7.77	16	7.23	1.57 - 33.34
	≥21.2 to <23.3	96	612.5	6	1.00 (reference)		2	1.00 (reference)	
	≥23.3 to <25.8	105	670.5	12	1.16	0.41 - 3.24	9	3.31	0.67 - 16.41
	≥25.8	113	708.9	21	2.49	0.96 - 6.47	12	4.95	1.05 - 23.35
	p for trend					0.85			0.57
	p for trend in women with BMI ≥21.2					0.02			0.031
ER-/PgR-									
	<21.2	46	295.2	14	0.95	0.41 - 2.20	10	0.90	0.35 - 2.29
	≥21.2 to <23.3	50	350.7	12	1.00 (reference)		11	1.00 (reference)	
	≥23.3 to <25.8	41	265.0	13	0.72	0.30 - 1.75	13	0.88	0.35 - 2.21
	≥25.8	37	241.9	11	0.94	0.38 - 2.33	9	1.00	0.38 - 2.64
	p for trend					0.77			0.91
	p for trend in women with BMI ≥21.2					0.96			0.98
ER + or PgR + v ER-/PgR- p for heterogeneity of trends						0.80			0.61
ER + or PgR + v ER-/PgR- p for heterogeneity of trends in women with BMI ≥21.2						0.10			0.13

[a] Adjusted by age, stage (in situ or localized, lymph node metastasis, local invasion, distant metastasis, missing), radiation therapy (no, yes), chemotherapy (no, yes), endocrine therapy (no, yes), smoking (current, past, never, missing), family history of breast cancer in father, mother, brother or sister (no, yes), menopausal status (premenopausal, postmenopausal, missing), physical activity (almost no, more than one hour per week, missing) and comorbidities (no, yes).
Among women with ER + or PgR + tumors, BMI was significantly associated with both all-cause and breast cancer-specific death in those with BMI ≥21.2 kg/m^2, and lighter (BMI <21.2 kg/m^2) women also had a higher risk of all-cause and breast cancer-specific death.

women with hormone receptor-positive tumors [9,10]. Several hypotheses to explain why obese breast cancer patients show poorer survival can be considered. Firstly, there may be differences in sensitivity to estrogen among tumors with different types of hormone receptors. A previous study found that hormone receptor-positive tumors showed a better response to endocrine therapy than ER-/PgR- tumors [34], indicating that ER + or PgR + tumors are the most sensitive to estrogen hormone. Secondly, it has been postulated that higher estrogen concentrations may confer increased biological aggressiveness on hormone receptor-positive tumors, as BMI is directly related to circulating estrogen levels [22,35,36]. Thirdly, higher BMI is associated with upregulation of a number of cellular proliferation pathways [37]. Consequently, obesity might lead to an increase of tumor cell proliferation and metastasis through undefined adipokine effects on tumor cells [17]. For example, leptin, an adipocytokine, is produced mainly by adipose tissue and is known to act as a cancer growth factor [38], as well as promoting angiogenesis and potentially stimulating the growth of breast cancer cells, thus possibly leading to reduced patient survival [39].

Our present multivariate-adjusted analysis showed that BMI <21.2 kg/m^2, i.e. low BMI, was associated with elevated risks of both all-cause and breast cancer-specific death among women with ER + or PgR + tumors. The relationship between low BMI and higher cancer mortality risk might be at least partly explained by the presence of circulating tumor cells (CTCs) in the peripheral blood of patients [40]. CTCs are derived from clones in the primary tumor [41] and are thought to become scattered to various organs, leading to the development of distant metastasis [42]. In patients showing chronic undernutrition, cytokine reactions and subsequent activation of the immune system are compromised, which might affect the tumor-immune system interaction in distant organs [43]. In this study, the BMI <21.2 kg/m^2 category might have included undernourished patients as well as properly nourished, naturally lean patients. This may have partly contributed to the increased risk of all-cause and breast cancer-specific death. Another reason for the relationship between the BMI <21.2 kg/m^2 category and higher risk of cancer mortality might have been the slightly higher proportion of patients with advanced-stage breast cancer. Therefore, we attempted to analyze the data by omitting cases of advanced breast cancer. However, this analysis yielded almost the same results (data not shown).

The major strengths of the present study were that no subject was lost to follow-up during the study period. The MCCH Cancer Registry conducts active follow-up by accessing hospital visit records, resident registration cards and permanent domicile data. In cases of death occurring outside the hospital, information on the date and cause of death was obtained with permission from the

Ministry of Justice. Another strength was the relatively low proportion of patients for whom data on hormone receptor status were missing (10.6%). In previous studies, the proportion of patients for whom data on ER and/or PgR status were missing ranged from 5.0% to 48.1% [2,4,9,10]. Distribution of receptor status for ER and PgR was roughly the same as those in previous studies which investigated 3,089 patients from ten hospitals in Japan [44]. A further strength was that it gave consideration not only to clinical stages but also to treatments such as chemotherapy, endocrine therapy and radiation therapy from an epidemiological viewpoint.

Several limitations of our study should also be considered. First, although BMI has been accepted as an index of obesity, it cannot be used to identify the distributions of fat and muscle tissue. Second, we used self-reported BMI at the baseline, and there may have been a misclassification of exposure due to self-reported weight and height. However, the self-reported current height and weight data were highly correlated with measured data, and therefore any possible bias was likely small. Third, stratification by hormone receptor status may have resulted in false positive or false negative results. The 95% CIs were wide for HRs by hormone receptor status, suggesting that statistical power might be limited because of relatively small number of patients and all-cause and breast cancer-specific deaths. To obtain reliable results with this stratification, subsequent recruitment of patients and follow-up will be required. Fourth, the generalizability of our results to the Japanese population as whole may be limited because our study was conducted among a population living in a rural area. More studies are needed to verify our results instead of to assess the generalizability.

Conclusions

In conclusion, being obese is a risk factor for all-cause death in premenopausal women and a risk factor for all-cause and breast cancer-specific death in patients with ER + or PgR + tumors. Lower BMI is associated with higher all-cause and breast cancer-specific death in patients with ER + or PgR + tumors. As higher and lower BMI are directly related to mortality [45], it is important to maintain an appropriate body weight for height.

Abbreviations

MCCH: Miyagi Cancer Center Hospital; ER: Estrogen receptor; PgR: Progesterone receptor; EIA: Enzyme immunoassay; IHC: Immunohistochemistry; HSCORE: Histology score; HR: Hazard ratio; CI: Confidence interval; CTC: Circulating tumor cell.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

MK, YM, YN, YK participated in the design of the study. MK, YM participated in the statistical analysis of the data. MK, YM, KF, YN, NO, YK drafted the manuscript. MK, YM, KF, YN, YK participated in the collection of the data. All authors read and approved the final manuscript.

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Breast Ultrasonographic and Histopathological Characteristics Without Any Mammographic Abnormalities

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Objective: We evaluated ultrasonographic findings and the corresponding histopathological characteristics of breast cancer patients with Breast Imaging Reporting and Data System (BI-RADS) category 1 mammogram.
Methods: We retrospectively reviewed the ultrasonographic findings and the corresponding histopathological features of 45 breast cancer patients with BI-RADS category 1 mammogram and 537 controls with mammographic abnormalities. We evaluated the ultrasonographic findings including mass shape, periphery, internal and posterior echo pattern, interruption of mammary borders and the distribution of low-echoic lesions, and the corresponding histopathological characteristics including histological classification, hormone receptor and human epidermal growth factor receptor 2 status of invasive ductal carcinoma and ductal carcinoma *in situ*, histological grade, mitotic counts and lymphovascular invasion in individual cases of BI-RADS category 1 mammograms and compared with those of the control group.
Results: The ultrasonographic characteristics of the BI-RADS category 1 group were characterized by a higher ratio of round shape ($P < 0.001$), non-spiculated periphery ($P = 0.021$), non-interruption of mammary borders ($P < 0.001$) and non-attenuation ($P = 0.011$) compared with the control group. A total of 52.6% of low-echoic lesions were associated with spotted distribution in the BI-RADS 1 group, whereas 25.8% of low-echoic lesions were associated with spotted distribution in the control group ($P = 0.012$). As for histopathological characteristics, there was a statistically higher ratio of triple-negative subtype ($P = 0.021$), and this particular tendency was detected in histological grade 3 in the BI-RADS category 1 group ($P = 0.094$).
Conclusion: We evaluated ultrasonographic findings and the corresponding histopathological characteristics for BI-RADS category 1 mammograms and noted significant differences among these findings in this study. Evaluation of these ultrasonographic and histopathological characteristics may provide a more accurate ultrasonographic screening system for breast cancer in Japanese women.

Key words: breast US – BI-RADS category 1 mammogram – histopathological characteristics

INTRODUCTION

The incidence of breast cancer has increased worldwide, which is partly considered to be due to mass screening programs resulting in the discovery of clinically occult or early breast lesions (1). Early clinical detection of breast cancer through screening has therefore led to the detection of the tumor at a relatively earlier clinical stage. The effectiveness of screening mammography on reduction in mortality by breast cancer has been well established in both Western countries and Japan (2). Mammography has thus become the gold standard for

detecting breast disorders. Therefore, it has become very important to increase the rate of mammographic screening among the general public toward reducing the breast cancer mortality. However, it is also true that 7.2% of the malignant cases were associated with no mammographic abnormalities (3). In addition, the malignant ratio of 20, 30 and 40 years without mammographic abnormalities was statistically higher than the ratio of the other age groups (3). Ultrasonography (US) has been in general proposed to prove much more effective in the detection of breast cancer if the patient is young, has dense breast or their detected masses are small (4–6). Therefore, it has become very important to improve the quality of US diagnoses.

The effectiveness of ultrasound screening for women aged 40 years has been evaluated in detecting and reducing mortality of the breast cancer in Japan in order to complement this particular pitfall of mammography (7). This study named J-START (The Japan Strategic Anti-cancer Randomized Trial) evaluates the effectiveness of screening mammography with US breast cancer screening compared with mammography alone in 40 years, with a design to study 50 000 women with mammography and US and 50 000 controls with mammography only (7). The participants are scheduled to take a second-round screening with the same modality 2 years onwards (7). The primary endpoints are sensitivity and specificity, and the secondary endpoint as the rate of advanced breast cancer (7). Whether or not breast US screening is adopted in the future large-scale screening therefore largely depends on the results of this research. Considerable efforts will be required to successfully carry out this massive undertaking done in Japanese population.

Strict or rigorous conformity to high quality of interpretation of US finding among those involved in this screening is therefore mandatory for the very success of an US diagnosis in such a large scale. We previously examined the correlation between US findings and the corresponding histopathological features in breast disorders in our previous study (6). There have been relatively few reported studies on assessing US performance and its resolution without any mammographic abnormalities (8). Therefore, in this study, we evaluated US findings and the corresponding histopathological characteristics for breast cancer patients with Breast Imaging Reporting and Data System (BI-RADS) (9) category 1 mammogram.

PATIENTS AND METHODS

Patients

We retrospectively reviewed the US findings and their corresponding histopathological features of 45 breast cancer patients with BI-RADS category 1 mammogram and 537 controls with mammographic abnormalities. The patients underwent needle biopsies or surgical resection at the Tohoku University Hospital from January 2006 to December 2010. We received informed consents from all the patients and the protocol for this study was approved by the Ethics Committee at Tohoku University Graduate School of Medicine.

Imaging Devices and Breast Tissue Specimens

The US examinations were assessed by one of the experienced eight breast specialists in Tohoku University Hospital. The consensus meeting of US was held for 1 whole week in order to standardize the US examination among these eight doctors. In addition, two of them independently evaluated the US findings in a retrospective manner, without the knowledge of clinical and histopathological information of individual patients. All US evaluations were carried out using Aloka SSD 3500 and ProSound α7 (Aloka Co., Tokyo, Japan) with a 10 MHz transducer.

We stained the corresponding tissue slides of the cases using hematoxylin–eosin (H&E) and immunohistochemistry for estrogen receptor (ER) and human epidermal growth factor receptor 2 (HER2). Surgical specimens had been fixed in 10% formaldehyde solution, cut into serial 5 mm-thick slices, embedded in paraffin, cut into 4 μm-thick sections and placed on the glue-coated glass slides. We employed the avidin–streptavidin immunoperoxidase method using the clone 6F11 antibody (Ventana, Tucson, AZ, USA) in automated immunostainer (Benchmark System; Ventana). A standardized immunohistochemistry kit (HercepTest for Immunoenzymatic Staining; Dako, Copenhagen, Denmark) was used for HER2 staining. Histopathological slides were reviewed by two pathologists independently without the knowledge of clinical information. Olympus (Tokyo, Japan) BX50 and 20× objectives were used for the analyses.

Imaging and Histopathological Analyses

Two or more hardcopy transverse and sagittal plane images of breast lesions were analyzed in this study. We recorded tumor shape, periphery, internal and lateral echo pattern, interruption of mammary borders and the distribution of low-echoic lesions, according to the BI-RADS sonographic classification (9) and the Japan Association of Breast and Thyroid Sonology (JABTS) breast sonographic classification (10). Tumor shape was tentatively classified into round, oval, lobular and irregular (9,10). Periphery was tentatively classified into circumscribed, obscured, indistinct and spiculated (9,10). Internal echo was classified into low and heterogeneity or high (9,10). Lateral echo was also classified into accentuation, no change and attenuation (9,10). Interruption of mammary borders was classified into interruption, indeterminate and no (9,10). Distribution of low-echoic lesions was classified into spotted and segmental (9,10) (Fig. 1).

Two of the experienced pathologists independently evaluated surgical pathology specimens, respectively. Histopathological evaluations were based on World Health Organization (WHO) histological classification of tumor of the breast (11) and Rosen's breast pathology (12). ER was determined by nuclear staining graded from 0 to 8 using the Allred score, and ER positivity was Grade 3 or more (13). With regard to HER2 evaluation, membranous staining was graded as the following: score 0–1+, 2+ and 3+ (14).

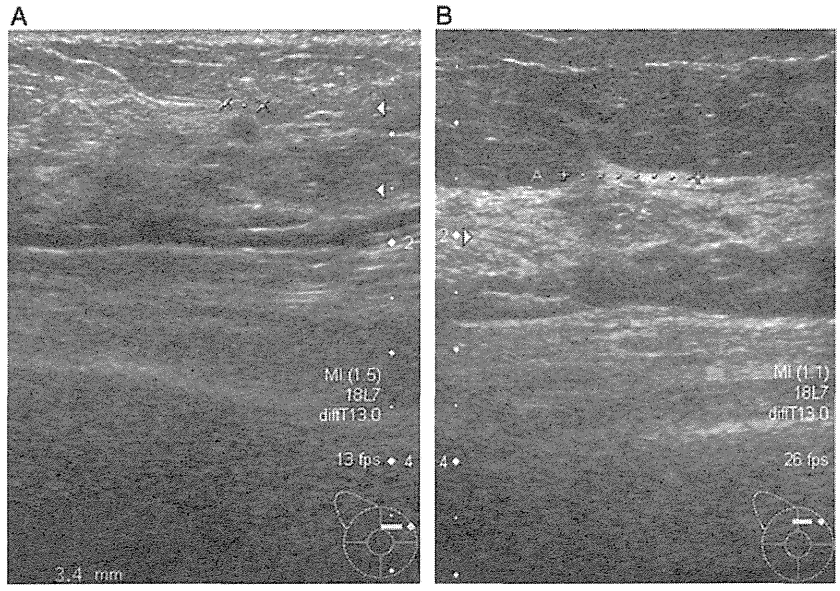

Figure 1. Representative illustrations of the distribution of low-echoic lesions. (A) Spotted and (B) segmental.

Scoring of 2+ was added fluorescence *in situ* hybridization (FISH) that was used to calculate the gene copy ratio of HER2-to-CEP17 (the PathVysion HER2 DNA Probe Kit; Abbott, Chicago, IL, USA). Positive is defined as either HER2:CEP17 signal ratio (FISH score) >2.2 (14). Histological grades and mitotic counts were assessed according to the criteria of Elston and Ellis (15). Van Nuys classifications were also assessed for ductal carcinoma *in situ* and invasive ductal carcinoma (IDC) with predominant intraductal components cases (16,17). We also identified the presence or absence of lymphovascular invasion according to the Rosen's Breast Pathology (12).

At first, we examined the differences of the patients' characteristics between these two groups including the distribution of age, menopausal status, past history of the benign proliferative disease, background of detection, clinical stage, breast density of mammography according to the BI-RADS lexicon (9) and surgical strategy as the breast-conserving ratio. We evaluated the US findings including mass shape, periphery, internal and posterior echo pattern, interruption of mammary borders and the distribution of low-echoic lesions and compared them with histopathological characteristics including histological classification, hormone receptor and HER2 status of IDC, tumor size confirmed by histopathology, histological grade, mitotic counts and lymphovascular invasion of BI-RADS category 1 mammograms. We then compared these findings with those of control group patients.

Statistical Analyses

Statistical analyses were performed using StatMate III for Windows ver. 3.18 (ATMS, Tokyo, Japan). The results were considered significant at $P < 0.05$.

RESULTS

The Details of Both BI-RADS 1 and Control Groups

Table 1 summarizes the difference in the patients' characteristics including the distribution of age, menopausal status, past history of the benign proliferative disease, background of detection, clinical stage, breast density of mammography and surgical strategy. The median ages of the study group and the control group were 48 years (range, 32–84) and 56 years (range, 26–88), respectively ($P = 0.047$). There was a statistically significant higher ratio of Stages 0 and I, heterogeneously and extremely dense, and conserving surgery in the BI-RADS 1 group ($P < 0.001$, <0.001 and 0.002, respectively). However, there was a statistically significant lower ratio of menopause and self-palpation in the BI-RADS 1 group ($P < 0.001$, respectively; Table 1).

Table 1. The details of patients

	BI-RADS 1	Control	*P* value	Odds ratio
Age	48 (32–84)	56 (26–88)	0.047	—
Menopausal ratio	37.8%	63.4%	<0.001	0.31
Benign proliferative disease	2.2%	9.5%	NS	2.34
Cause of detection (self-palpation ratio)	24.4%	59.4%	<0.001	0.22
Stage (Stages 0 and I)	93.3%	66.4%	<0.001	7.08
Heterogeneously and extremely dense ratio	91.1%	39.1%	<0.001	15.97
Surgical strategy (conserving ratio)	95.6%	74.6%	0.002	7.82

The Ratios of Mass Cases and the Tumor Size

Twenty-six out of the 45 were US mass cases in the BI-RADS 1 group and 370 out of the 490 were US mass cases in the control group. There was a statistically significant difference between the BI-RADS 1 and control groups ($P = 0.003$). The US tumor size of BI-RADS 1 and control groups was 12.1 mm (range, 3.2–24.9 mm) and 18.5 mm (range, 6.5–150 mm) with statistically significant differences ($P < 0.001$).

Evaluation of the US Characteristics

Figure 2 summarizes the results of the numbers and ratios of mass shape (Fig. 2A), periphery (Fig. 2B), internal echo pattern (Fig. 2C), lateral echo pattern (Fig. 2D) and interruption of mammary borders (Fig. 2E) of the BI-RADS 1 and control groups. There were statistically higher ratios of round mass shape ($P < 0.001$), no change of lateral echo pattern ($P = 0.028$) and no or indeterminate interruption of mammary borders ($P < 0.001$) in the BI-RADS 1 group. There were statistically lower ratios of spiculated periphery ($P = 0.021$), attenuation of lateral echo pattern ($P = 0.011$) and interruption of mammary borders ($P < 0.001$) in the BI-RADS 1 group. Figure 3 summarizes the results of the numbers and ratios of distribution of low-echoic lesions. There were statistically higher ratios of spotted distribution and lower cases of segmental distribution in the BI-RADS 1 group than in the control group ($P = 0.012$).

Evaluation of the Corresponding Histopathological Characteristics

Figure 4 summarizes the results of the numbers and ratios of results classified by histological subtypes (Fig. 4A), hormone receptor and HER2 expression of IDC (Fig. 4B), tumor size of the invasive lesion as confirmed by the histopathological examination (Fig. 4C), histological grade (Fig. 4D), mitotic counts (Fig. 4E) and lymphovascular invasion (Fig. 4F). There was statistically higher ratios of triple-negative subtype, smaller tumor size and lower case of lymphovascular invasion in the BI-RADS 1 group ($P = 0.021$, $P < 0.001$ and $P = 0.012$, respectively) compared with the control group. In addition, a higher ratio of histological grade 3 was detected in the BI-RADS 1 group but this difference did not reach the statistical significance ($P = 0.094$).

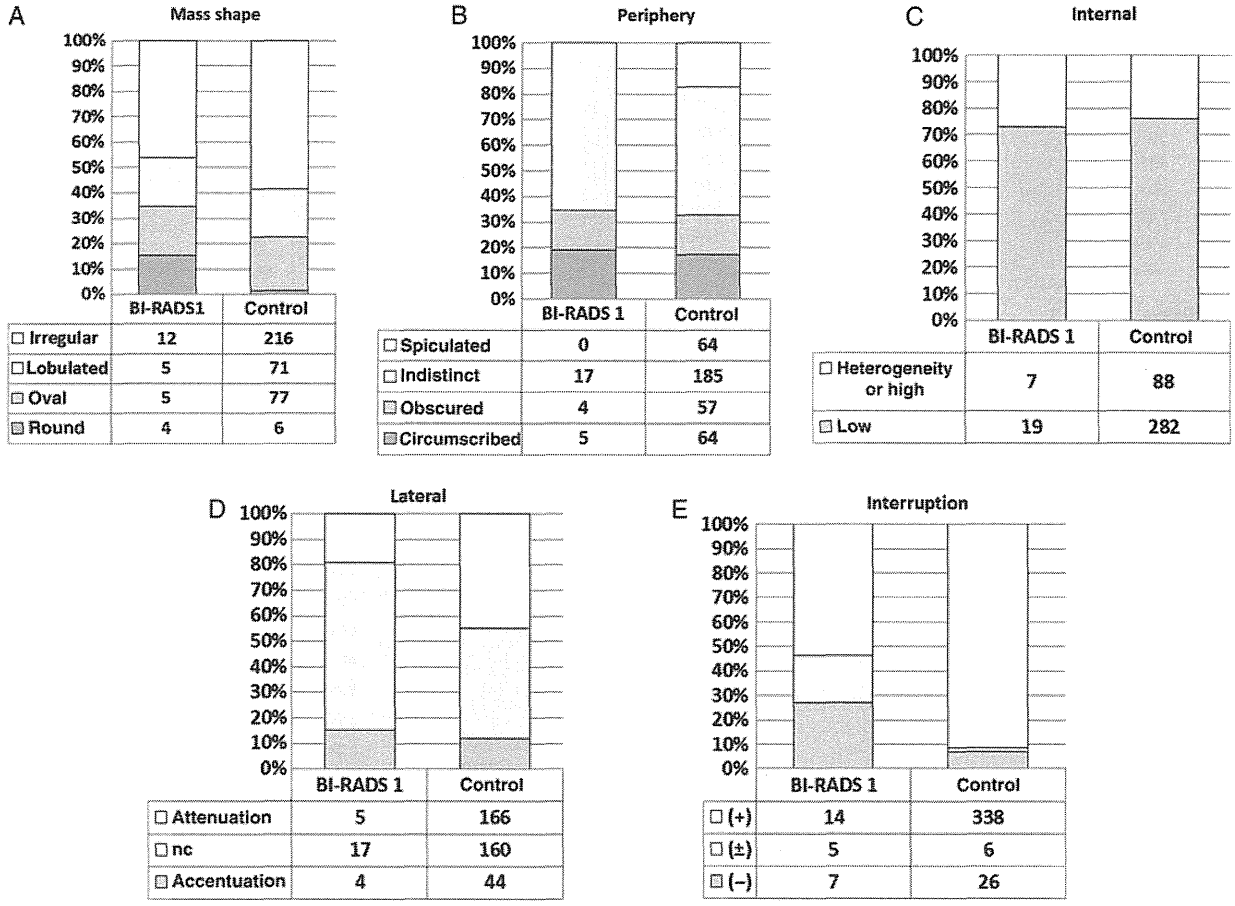

Figure 2. The US characteristics of BI-RADS category 1 and control groups. (A) Mass shape, (B) periphery, (C) internal echo pattern, (D) lateral echo pattern and (E) interruption of mammary borders.

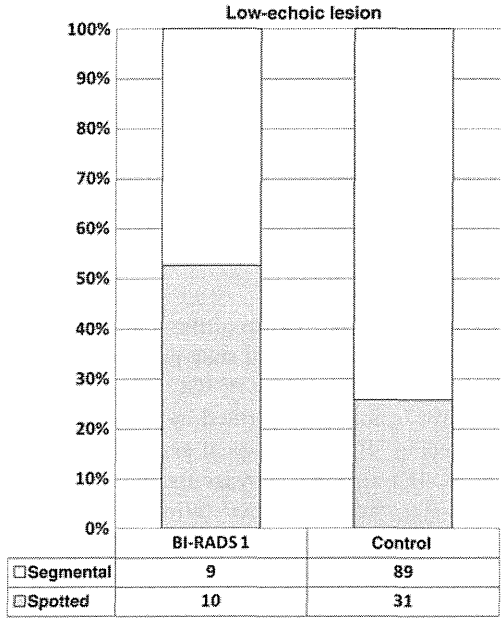

Figure 3. The distribution of low-echoic lesions of BI-RADS category 1 and control groups.

DISCUSSION

Mammography has been considered a gold standard for breast cancer screening system. However, US screening combined with mammography may have the potential to become one of the useful screening systems to decrease breast cancer mortality according to the results of the J-START trial (7). Therefore, strict or rigorous conformation to high quality of interpreting the US findings is required or mandatory for the future success of an US diagnosis especially at the level of mass screening. Our present study is the first study to focus upon incremental detection of breast cancer by US in asymptomatic women with mammography-negative breasts, and focused on the US findings and the corresponding histopathological characteristics of the cases with BI-RADS category 1 mammograms.

US detected cancers are in general smaller than those identified with mammography. Results of our present study demonstrated that the BI-RADS category 1 group was associated with a statistically higher ratio of low-echoic lesions than the control group. In addition, 52.6% of low-echoic lesions demonstrated spotted distribution in the BI-RADS 1 group, whereas 25.8% of low-echoic lesions spotted

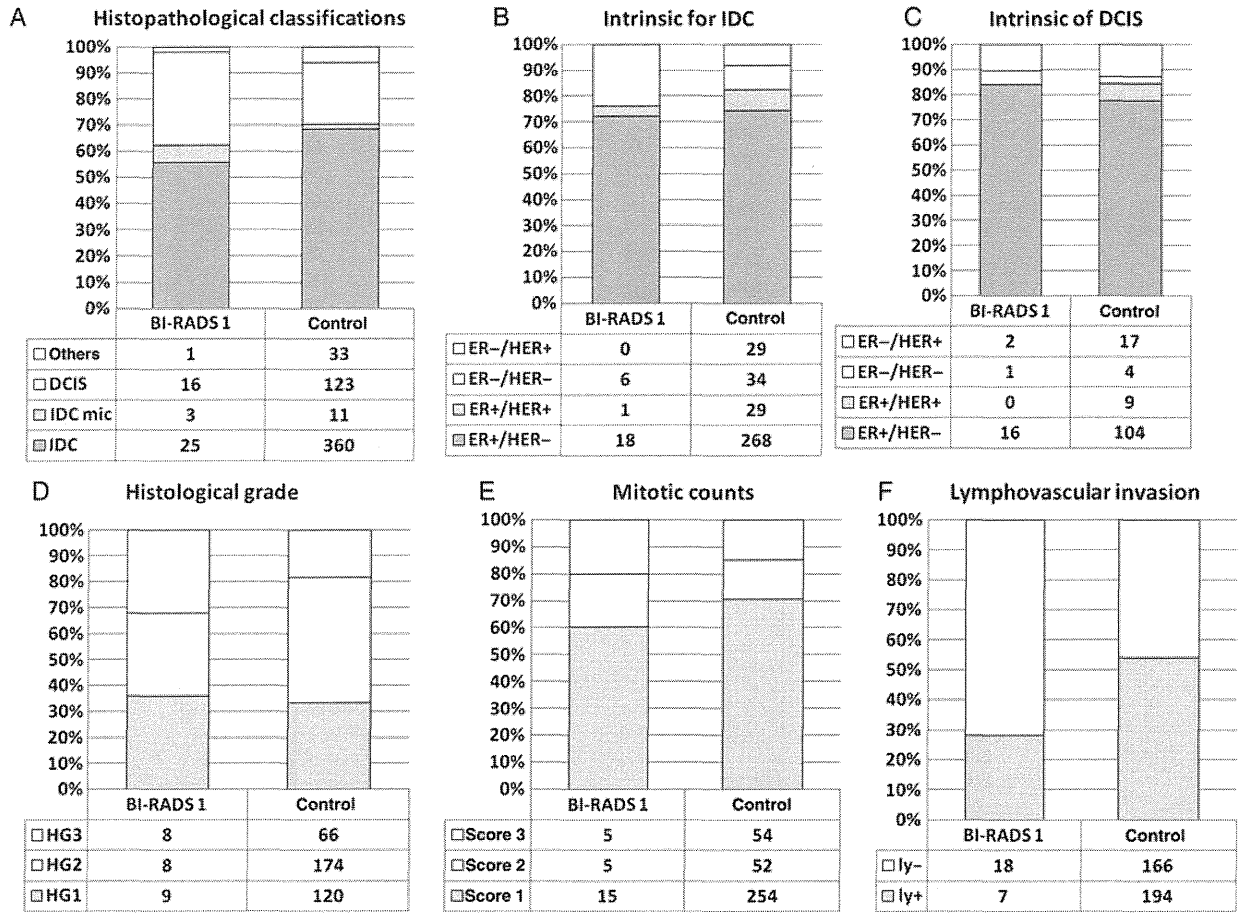

Figure 4. The histopathological characteristics of BI-RADS category 1 and control groups. (A) Histological classification, (B) hormone receptor and human epidermal growth factor receptor 2 expression of invasive ductal carcinoma, (C) tumor size of the invasive lesion, (D) histological grade, (E) mitotic counts and (F) lymphovascular invasion.

distribution in the control group. A low-echoic lesion with spotted distribution is therefore considered one of the predicting factors of malignancy in the BI-RADS category 1 group. In addition, the tumor size of the BI-RADS 1 group was smaller, and the detected masses were characterized by a higher ratio of round shape, non-spiculated periphery, non-interruption of mammary borders and non-attenuation in the BI-RADS category 1 group. These results could be mainly affected by mammographic breast density. In addition, results of our present study also demonstrated that there was a statistically higher ratio of heterogeneously and extremely dense breast in the BI-RADS 1 group and the tumors with well-collagenized stromal reaction were also detected as architectural distortion or spiculation in dense breast mammogram. Therefore, mammographic breast density was reasonably postulated to influence characteristics of breast cancers with BI-RADS category 1. Results of previous studies demonstrated that the most breast cancer cases of BI-RADS category 1 were relatively hypoechoic within a background of hyperechoic fibroglandular tissue, which may make the lesions more conspicuous and detectable (18). However, it is also true that previous studies have not evaluated the US findings of BI-RADS category 1 cases and this is the first study demonstrating the US findings such as mass shape and periphery of BI-RADS category 1 cases. In addition, this is the first reported study to demonstrate histopathological characteristics of BI-RADS category 1 cases. The statistically higher ratio of triple-negative subtype was detected in BI-RADS category 1 cases, and histological grade 3 tended to be also higher in the BI-RADS category 1 group. Results above did indicate that the BI-RADS category 1 group was histologically characterized by a higher malignant level than those with mammographic abnormalities, but it awaits further investigations for clarification.

Previous study also demonstrated that earlier detection of breast cancer resulted in a decrement in mortality, which parallels the reduction in size distribution of cancers depicted and closely parallels the reduction in rates of node-positive breast cancer (19). Screening US also appears to detect many breast cancer cases at a smaller size and earlier stage compared with mammographic screening. In addition, in women with mammography dense breast, US was reported to be able to detect a substantially larger number of cancers with a supplemental cancer detection of 0.3–0.5% by US alone (18). Therefore, it is important to detect the US findings with the localized low-echoic lesion. In addition, among the BI-RADS category 1 group, particular attention should be paid to the US findings such as solidary differentiated masses such as oval or round shape and non-spiculated periphery because the corresponding histopathological features of the cases associated with these US findings above include a much higher ratio of triple-negative subtype and/or histological grade 3. Therefore, early detection of such solidary masses with triple-negative subtype and/or high histological grade by US may possibly contribute to the eventual reduction in breast cancer mortality.

We evaluated US findings and the corresponding histopathological characteristics for BI-RADS category 1 mammograms and noted significant differences among these findings in this study. Evaluation of these US and histopathological characteristics may provide a more accurate US screening system for Japanese women.

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Conflict of interest statement

None declared.

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Usefulness of presentation of similar images in the diagnosis of breast masses on mammograms: comparison of observer performances in Japan and the USA

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Abstract Computer-aided diagnosis has potential in improving radiologists' diagnosis, and presentation of similar images as a reference may provide additional useful information for distinction between benign and malignant lesions. In this study, we evaluated the usefulness of presentation of reference images in observer performance studies and compared the results obtained by groups of observers practicing in the United States and Japan. The results showed that the presentation of the reference images was generally effective for both groups, as the areas under the receiver operating characteristic curves improved from 0.915 to 0.924 for the group in the US and from 0.913 to 0.925 for the group in Japan, although the differences were marginally ($p = 0.047$) and not ($p = 0.13$) statistically significant, respectively. There was a slight difference between the two groups in the way that the observers reacted to some benign cases, which might be due to differences in the population of screenees and in the socio-clinical environment. In the future, it may be worthwhile to investigate the development of a customized system for physicians in different socio-clinical environments.

Keywords Similar images · Computer-aided diagnosis · Breast masses · Mammograms · Image retrieval · Observer study

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1 Introduction

Breast cancer is the most frequently diagnosed cancer and one of the leading causes of cancer deaths in women in Japan, the United States (US), and European countries [1–3]. Mammography is considered the most effective screening method for early detection of breast cancer for women at normal risk [4–6]. For improving the diagnostic accuracy and efficiency, computer-aided detection (CADe) was introduced [7–10], and its potential usefulness was indicated in an observer performance study [11] and in prospective studies [12–16]. Once a suspicious lesion is found, radiologists may determine whether it should be biopsied or followed up. However, diagnosis on mammograms can be difficult and requires proper training and reading experience. For assisting radiologists' reading, investigators have suggested computer-aided diagnosis (CADx), in which a computer provides the likelihood of malignancy of an unknown lesion and have reported the potential usefulness of CADx in distinguishing between benign and malignant lesions on mammograms [17–19]. In these studies, radiologists' performance in terms of the area (AUC) under the receiver operating characteristic (ROC)

curve was improved with use of CADx; however, the studies indicated that the AUCs by many observers with CADx were lower than the AUC by the computer alone. One of the reasons might be that the result of computer analysis was summarized only in one numeral, i.e., the likelihood of malignancy, and the evidence was not clear to radiologists.

In recent years, mammography practice has been shifting from analogue to digital images. With implementation of Picture Archiving and Communication System (PACS), it became much easier to store and retrieve images from the previous examinations, and an effective use of stored data is expected. Radiologists, on the other hand, are trained and gain experience by reading many images in their clinical practice, in textbooks, and in training courses. Therefore, presentation of images that are similar to an unknown image can be an intuitive guide to reinforce the numerical likelihood of malignancy [20]. Different methods for automated selection of similar images have been investigated for diagnosis of chest radiographs [21, 22], thoracic computed tomographs [23, 24], and mammograms [25–31]. In some studies, reference images were selected on the basis of the predicted diagnosis [21, 22, 27, 28], whereas in other studies, images were selected by the similarity of the feature values [24, 26, 28]. For selecting similar images from the point of view of diagnosis, we have been investigating a method for quantifying the subjective ratings by radiologists [29, 30], as well as, a similarity index that takes into account the subjective similarity rated by radiologists [23, 31–33]. In our method, the similarity measure, called a psychophysical measure, was determined using an artificial neural network (ANN) which would be trained to learn the relationship between the subjective similarity ratings by radiologists and the computer-extracted image features.

Some of the above studies have indicated the potential usefulness of providing reference images together with other information such as the predicted diagnosis [22–24, 27, 34]. In these studies, it was not clear whether the presentation of reference images itself or the both images and other information together was helpful. Therefore, in order to evaluate the usefulness of providing similar images and to investigate the effect on radiologists in detail, we conducted the observer performance study to evaluate the radiologists' abilities in distinguishing between benign and malignant masses without and with similar images [35]. The result of this study was that, although the presentation of similar images provided beneficial effects, the average AUC was almost unchanged. One of the important findings in this study was that a reference image database must be carefully created so that it does not include "confusing" cases. When textbook-type cases are shown, radiologists will feel comfortable and can confidently and properly react to the given information. However, when atypical cases are presented, radiologists may become anxious, especially if they are cases of cancer. Another finding was that when a new case in question may be a benign-looking malignant case or a malignant-looking benign case, similar images would not be helpful. For these cases, radiologists' initial assessment is likely to be incorrect, and the presentation of similar images would only reinforce their incorrect decisions. This effect is, in fact, one that any type of CADx could have in common. When radiologists' initial judgment for a malignant-looking benign lesion was malignant, and the computer-estimated likelihood was also malignant, radiologists would become confident of their incorrect decision.

In this paper, we report the result from our second observer study after manual refinement of the database to exclude confusing cases. A group of radiologists practicing in the US and another group of radiologists and breast surgeons in Japan participated in the observer study, and the results from the two groups were compared.

2 Materials and methods

2.1 Case selection

Regions of interest (ROIs) including breast masses were used in this study. They were obtained from the Digital Database for Screening Mammography (DDSM) [36], which was made available by the University of South Florida. We initially collected 1568 ROIs, including 728 malignant and 840 benign masses [31]. ROIs containing microcalcifications which may influence the diagnosis of masses were excluded from the database. In the previous observer study [35], potentially confusing cases (benign-looking malignant and malignant-looking benign masses) were excluded from the reference database, which consisted of 365 malignant and 442 benign masses, by use of the computer-estimated likelihood of malignancy. However, because of the imperfect accuracy of the estimated likelihood, the database was suboptimal. In this study, for creating a better reference database, all of the cases were rated by a co-author (C.M.) for their difficulty in distinguishing between benign and malignant from 1 to 4, with 1 being difficult and 4 being easy. The images with unclear masses or with low quality that may not be helpful when presented as a reference were rated 0.

For the observer study, 100 cases, including 50 malignant and 50 benign masses, were selected from those rated 2, 3, and 4 to serve as study cases (unknown cases). They were selected by stratified randomization according to the size distributions of the database with 2.5 mm size bins, excluding those less than 5 mm and those larger than

25 mm. After removing all of the ROIs obtained from the same patients that were selected as the unknown cases, the cases rated 3 and 4 comprised the reference database, which included 429 malignant and 480 benign mass ROIs.

For each unknown image, 8 images each from the malignant and benign groups were selected as "similar" reference images, although 4 images each were presented in the monitor, and the next 4 images were provided only if an observer requested it. In the selection of similar reference images, the size criterion of no more than 50 % difference in the effective diameters was applied first. From the remaining cases, reference images were selected on the basis of the psychophysical similarity measures, which were determined by the ANN trained with 300 sample pairs in the previous study [32]. In the training of the ANN, image features characterizing the shape, contrast, and margin were used as input, and the subjective similarity data by radiologists based on the overall impression for diagnosis were used as the teacher. For avoiding having the same image presented more than 5 times as the first 4 images in 100 cases, the top 10 images with the highest similarity measures were preselected, and 4 of them were used. Note that they were called the reference images because, in some cases, there may be no "similar" images with very high similarity measures, especially the benign reference images for the malignant unknown cases and the malignant reference images for the benign unknown cases.

2.2 Observer performance studies

Observer studies for evaluating the usefulness of presenting reference images in the distinction between benign and malignant masses were conducted at the University of Chicago, Chicago, USA, and at Nagoya Medical Center, Nagoya, Japan. During the studies, the images were shown on a monochrome liquid crystal display monitor (ME511L/P4, 21.3 in., 2048 × 2560 pixels, 410 cd/m^2 luminance; Totoku Electric Co., Ltd.). The readings were conducted in the sequential reading mode, in which an observer was asked to provide his/her confidence level of a lesion being malignant on a continuous rating scale from 0.00 to 1.00, corresponding to "definitely benign" and "definitely malignant," respectively. Immediately after the first rating, four "similar" benign images and four "similar" malignant images were presented on the right and left sides of the unknown case, and the observer was asked to reconsider his/her confidence level. If an observer requested it, next four benign and four malignant images would be shown.

The instructions to the observers were: (1) The purpose of this study is to investigate whether providing the similar known images can assist radiologists in the distinction between benign and malignant lesions on mammograms. (2) 100 unknown cases are included in this study. The training session including four cases is provided at the beginning of the study. (3) You are asked to provide your confidence level regarding the malignancy (or benignity) of a lesion with a bar displayed on the monitor by use of a mouse first without similar images, and then after observing the similar images. (4) For each unknown case, four most similar images each from benign and malignant lesions in the database are provided. If desired, you may observe additional four similar images by clicking a "show similar images 5–8" button. (5) There is no time limit.

Ten observers, including two attending breast radiologists, three breast imaging fellows, and five radiology residents, participated in the observer study in the US. The two attendings had 13 and 3 years of experience in reading mammograms, whereas the three fellows were in the first or second year of a breast imaging fellowship, and the residents were third- or fourth-year senior residents who had been trained in the breast-imaging section in their rotation. Eleven observers, including 10 radiologists and breast surgeons who were certified for breast image reading and one in training to be certified, participated in Japan. The ten certified physicians had a mean of 13 years of experience in reading mammograms. The results were evaluated by use of multi-reader multi-case (MRMC) ROC analysis (the University of Chicago, IL, USA) [37].

3 Results

The overall results indicated that AUCs without and with the presentation of the reference images were both high, probably because difficult cases were not included in this study. The AUCs without and with the reference images for the individual observers are listed in Table 1. The mean AUCs were slightly improved by providing the reference images, from 0.915 to 0.924 for the group in the US and from 0.913 to 0.925 for the group in Japan; however, the differences were not statistically significant for the Japan group and marginally significant for the US group. If a change in the confidence level of more than 0.1 in the direction of the correct diagnosis is considered a beneficial effect, on average, there were larger numbers of cases that the presentation of the reference images affected beneficially than those affected detrimentally. Figure 1 shows the numbers of beneficially and detrimentally affected cases for each observer. The average numbers of beneficially and detrimentally changed cases were 13 and 8, respectively, for the US group and 16 and 7, respectively, for the Japan group with p values of 0.04 and 0.01 by paired t test.

It may be noticed in the results that for the US observers, there were more beneficial effects to the malignant cases than to the benign cases, and the majority of the detrimental cases were benign cases. On the other hand, for the

Table 1 Areas under the receiver operating characteristic curves without and with the presentation of the reference images for the individual observers

Observers	US group		Japan group	
	Without	With	Without	With
A	0.951	0.962	0.939	0.942
B	0.972	0.978	0.893	0.924
C	0.940	0.938	0.936	0.947
D	0.947	0.942	0.969	0.941
E	0.942	0.943	0.880	0.880
F	0.906	0.931	0.888	0.919
G	0.874	0.877	0.879	0.888
H	0.887	0.913	0.905	0.958
I	0.871	0.874	0.918	0.940
J	0.863	0.885	0.901	0.885
K			0.936	0.952
Average (p value)	0.915	0.924 ($p = 0.047$)	0.913	0.925 ($p = 0.13$)

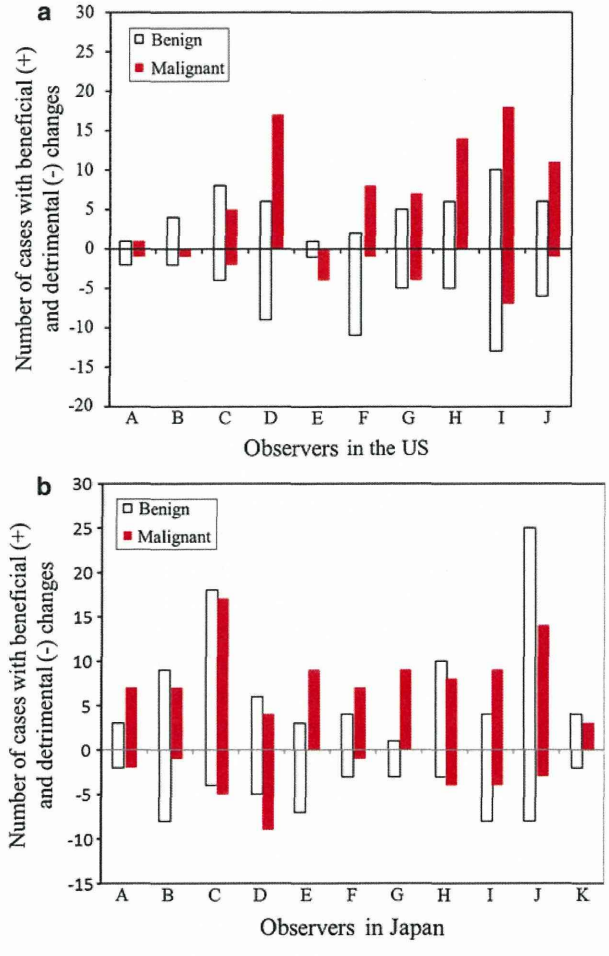


Fig. 1 Numbers of cases that the presentation of the reference images affected beneficially (positive) and detrimentally (negative) for the individual observers. **a** Observers in the US, and **b** observers in Japan

Japanese observers, the presentation of the reference images was helpful for both the malignant and the benign cases. Figure 2 shows the relationships between the average initial confidence levels and their changes, where positive changes correspond to the changes toward a correct diagnosis, for the two groups of observers. It is apparent in the figures that the presentation of the reference images had beneficial effects for many of the malignant cases. For the benign cases, however, it caused the US observers to increase their confidence levels toward malignant (indicated by an arrow in Fig 2a). The results indicate that some observers, regardless of their initial judgments as benign or uncertain, became worried after the reference images were presented. On the other hand, the average initial confidence levels for the benign cases by the Japanese observers were, on average, low for many cases, and the observers became confident of their judgment after the presentation of the reference images (indicated by an arrow in Fig 2b).

Figure 3 shows the relationship between the changes in the confidence levels before and after the presentation of the reference images by the two groups. The points in the right upper quadrant correspond to the cases in which the presentation of the reference images, on average, resulted in the beneficial changes for both groups of observers. An example of such cases is shown in Fig. 4. In this case, the unknown case was malignant. The initial judgments by the observers in both groups were mostly uncertain, and their confidence levels increased after the reference images were presented, with six of them increasing more than 0.1. On the other hand, there are some benign cases in the upper left quadrant in Fig. 3 for which the image presentation resulted in beneficial changes for the Japanese observers, but caused the detrimental changes for the US observers. Figure 5 shows one of such cases. In this case, the observers' initial judgments ranged from somewhat uncertain to likely benign, and the presentation of the reference images caused some US observers to increase their ratings, whereas most Japanese observers remained unchanged.

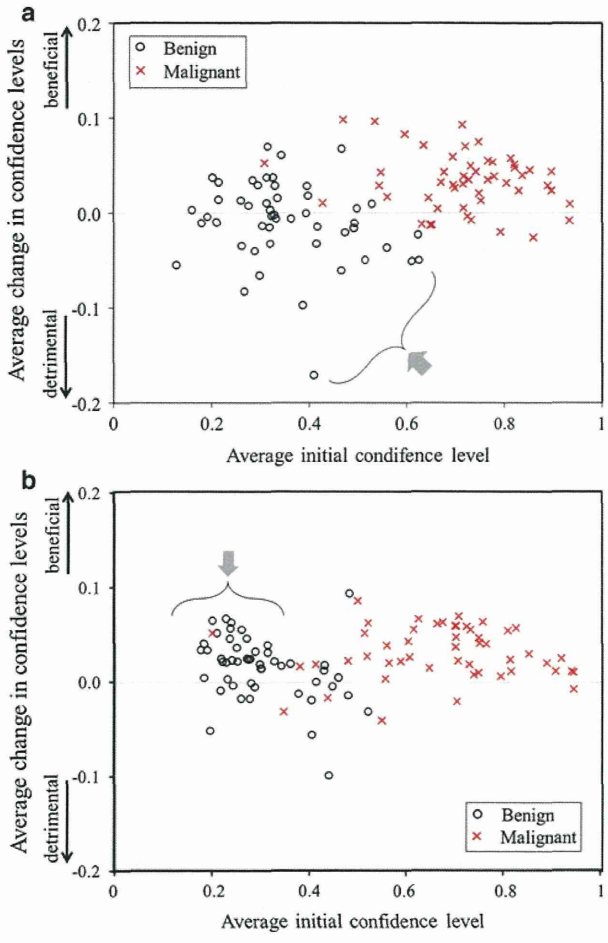


Fig. 2 Relationships between the average initial confidence levels and the changes in confidence levels toward (+) correct and (−) incorrect diagnosis by the **a** observers in the US and **b** observers in Japan. An *arrow* in **a** indicates the benign cases in which presentation of similar images caused detrimental effects, whereas an *arrow* in **b** indicates the benign cases in which the presentation caused beneficial effects

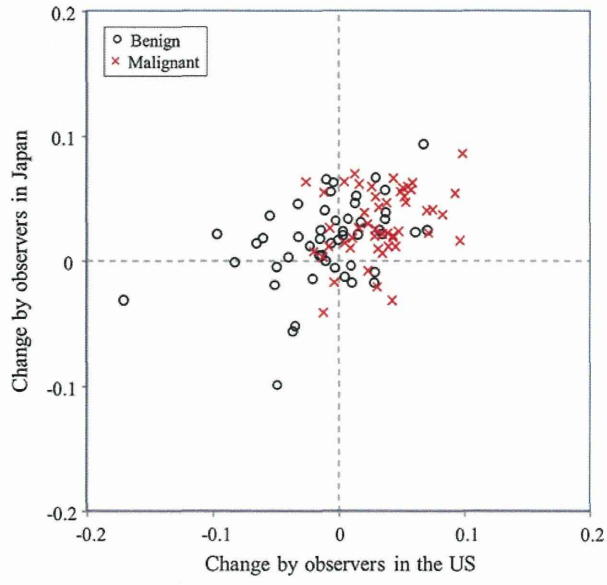
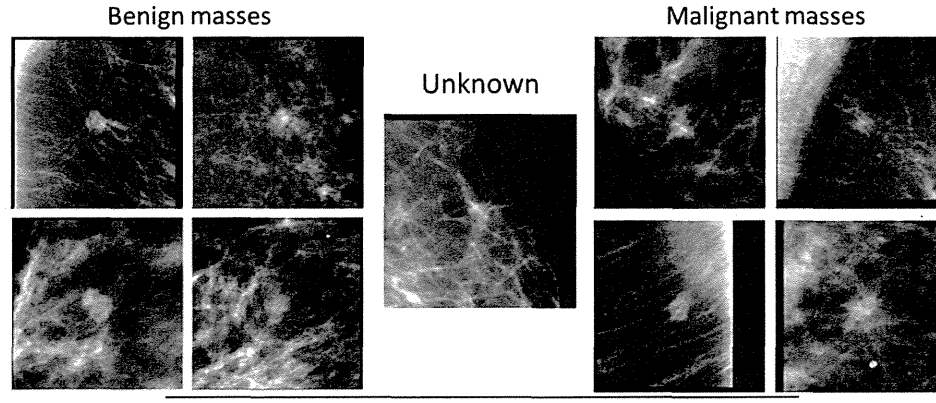


Fig. 3 Relationship between the changes in confidence levels before and after the presentation of the reference images between the two groups of observers

4 Discussion

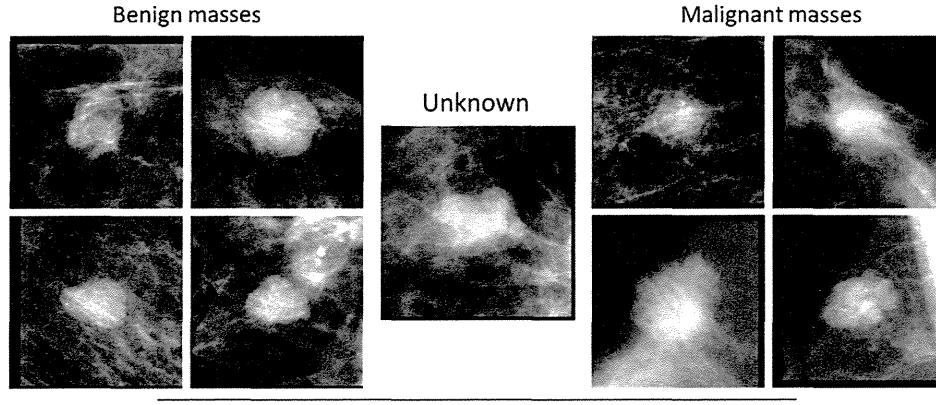
The results of the observer studies showed a somewhat notable difference between the practitioners in the US and those in Japan in the sense of their reaction when the reference images were presented. The differences between the two groups seemed more prominent in the benign than in the malignant cases. One difference we observed during the reading sessions and also obtained in the observers' feedback was that the practitioners in the US primarily and dominantly consider margin characteristics in distinguishing between benign and malignant masses, whereas the practitioners in Japan consider the density of the masses, which relates to their elasticity, in addition to the margin characteristics. This may be due to the fact that Japanese women tend to have dense breasts, and physicians have a difficult time assessing margins more often than those in the US. It is also related to the fact that the breast cancer incidence rate increases with age in the US, whereas it peaks around the late 40 s in Japan. Therefore, the observers in Japan often complained about the use of ROIs without the availability of whole mammographic views during the observer study. When they read mammograms, the relative mass density in comparison with the normal breast tissue density of the patient is one of the important factors that they consider. However, with the lack of a whole view, it was difficult to see the grandular tissue density of the whole breast and the symmetry against the opposite breast.

Another perspective could be related to the number of law suits on missed cancers in the US. Although nobody wants to miss a cancer, physicians in the US may be particularly sensitive to missing one. This is manifested in the reported higher recall rates in the US than those in other countries. According to the study by the Physicians Insurers Association of America, breast cancer is the subject of the most frequent malpractice lawsuits filed, in which 41 % of all claims resulted in compensation averaging about $438,000 [38]. Dick et al. [39] have reported that, in their surveys, about a half of US radiologists responded that they had had a malpractice claim filed against them. In Japan, based on the statistics by the Supreme Court (http://www.courts.go.jp/saikosai/iinkai/izikankei/index.html), the number of medical lawsuits in each year is about 1000, in which internal medicine, surgery, orthopedics, and gynecology are the top four



	Average change	Number of observers who changed
Observers in the US	0.10 (0.47 → 0.57)	3
Observers in Japan	0.09 (0.50 → 0.59)	3

Fig. 4 A malignant case in which the presentation of the reference images resulted in beneficial changes for the both groups



	Average change	Number of observers who changed
Observers in the US	-0.10 (0.39 → 0.48)	-5
Observers in Japan	0.02 (0.33 → 0.31)	1

Fig. 5 A benign case in which the presentation of the reference images resulted differently for the observers in the US and those in Japan

frequently filed, accounting for more than 60 % of cases; no number was provided for radiology. Although it is difficult to compare these statistics, it can be conjectured that US radiologists tend to practice more defensive medicine. The difference is also seen in the diagnostic assessment of probably benign lesions. In the US, cases assessed as BI-RADS 3, "probably benign finding", should have less than 2 % risk of malignancy, whereas a breast imaging guideline in Japan was created on the basis of the BI-RADS, and cases assessed as category 3 "benign but malignancy can't be ruled out" may have about a 2–10 % chance of cancer. These facts may explain the tendency of the US observers to give slightly higher ratings than those in Japan.

There were some differences in the years of experience between the two groups. It is difficult to determine whether the different reaction to the benign cases could be due to the years of experience, because US attending radiologists had a tendency to make only small changes in confidence levels. Note that the years of experience is one index; US attending radiologists and fellows only practice in breast imaging section in their routine work, whereas Japanese radiologists, although experts in breast image reading, may also read images of other organs, and surgeons may spend limited time in image reading. In addition, Japanese observers work at several different clinical facilities, and their practice may be somewhat different. The population of the test cases which were obtained in the US and primarily included Caucasians and African Americans may have affected the performance. Although the average years of experience and their background were different between two groups, the mean AUCs without and with similar images were comparable.

One of the limitations in this study was that we excluded difficult cases from the test dataset, which resulted in high AUCs both without and with similar images. Because of the limitation of time, the population of test cases selected for the observer performance studies were generally different from the clinical population. In this study, we excluded difficult cases because it was believed that CAD likely has no impact or detrimental effect on such cases. When a benign lesion looks very similar to typical malignant cases, a computer likely selects similar malignant lesions and outputs a high likelihood of malignancy. Even if a computer provided a low likelihood of malignancy, it is unlikely that radiologists would change their initial decision. Although we believe that such atypical cases are relatively rare, we did not include them in the present study because the number of the study cases was limited. As a result, the impact of the overall beneficial effect observed in this study could be much smaller in an actual clinical population. On the other hand, the high AUCs without similar images might have decreased the chances of gain.

5 Conclusion

The results of the observer studies indicate a potential utility of presenting reference images in the distinction between benign and malignant masses on mammograms by physicians. The overall effects in terms of the mean AUC were comparable for the observers in both counties. However, there was a slight difference in the reactions by the observers for some benign cases. This difference could be due to the differences in the patient population and the diagnostic environment in the two countries. In this study, the similarity measures used for the selection of reference images were based on the subjective similarity ratings determined by breast radiologists who practice in the US. Although subjective similarities noted by different groups of observers were expected to be comparable for most of the cases, there could be some differences in the impression due to the diagnostic environment. For improving the utility of computer-aided diagnosis systems, it may be worthwhile to investigate the development of a customized CAD system with an effective image selection scheme for physicians in different socio-clinical environments.

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