★J-STARTの目的
超音波による乳がん検診の精度と有効性を検証すること

★プライマリ・エンドポイント：
「感度・特異度及び発見率を２群間で比較する」

平成24年度でA1—A4までの2回目受診が完了するため、平成26年度までに1回目J-STARTの感度・特異度、発見率は算出することができる。

［問題点］

感度・特異度、発見率だけでは乳がん検診への導入への検討材料にはならない。検診としてのエビデンスは死亡率減少効果である。そのためには、下記セカンダリ・エンドポイントと死亡率の把握が必要である。

★セカンダリ・エンドポイント：
「追跡期間中の累積進行乳がん罹患率を２群間で比較する」

- 目的／介入群と非介入群での累積進行乳癌罹患率および乳がん死亡率を比較する
- 方法／①両群の参加者へ、２年に１度アンケート調査を実施し乳がん罹患を聞き取る（治療情報はご本人の同意を得たうえで医療機関から収集）
  ②両群の乳がん死亡を人口動態調査と地域がん登録により把握する
- 期間／平成25年4月から平成32年3月（予定）

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ORIGINAL ARTICLE

Harms of screening mammography for breast cancer in Japanese women

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Abstract
Background The US Preventative Services Task Force assesses the efficacy of breast cancer screening by the sum of its benefits and harms, and recommends against routine screening mammography because of its relatively great harms for women aged 40–49 years. Assessment of the efficacy of screening mammography should take into consideration not only its benefits but also its harms, but data regarding those harms are lacking for Japanese women.
Methods In 2008 we collected screening mammography data from 144,848 participants from five Japanese prefectures by age bracket to assess the harms [false-positive results, performance of unnecessary additional imaging, fine-needle aspiration cytology (FNA), and biopsy and its procedures].
Results The rate of cancer detected in women aged 40–49 years was 0.28%. The false-positive rate (9.6%) and rates of additional imaging by mammography (5.8%) and ultrasound (7.3%) were higher in women aged 40–49 years than in the other age brackets. The rates of FNA (1.6%) and biopsy (0.7%) were also highest in women aged 40–49 years. However, they seemed to be lower than the rates reported by the Breast Cancer Surveillance Consortium (BCSC) and other studies in the US.
Conclusions The results, although preliminary, indicate the possibility that the harms of screening mammography for Japanese women are less than those for American women.

Keywords Breast cancer screening · Harm · Mammography

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Introduction

Recent years have seen increased awareness of the need for assessment of the efficacy of cancer screening on the basis of both its benefits and harms [1–5]. The US Preventative Services Task Force (USPSTF) [3, 4] reported their updated guidelines for screening mammography. They comprehensively assessed the efficacy of breast cancer screening in terms of the net benefit, which is the sum of benefits (mortality reduction) and harms (radiation exposure, pain, anxiety, over-diagnosis, and false-negative and false-positive mammography results). For women in their 40s and 50s, screening mammography had a 15 and 14% mortality reduction effect as the benefit in eight and six meta-analysis studies [3]. On the other hand, the harms (especially false-positive mammography, unnecessary additional imaging tests and histological examinations) were relatively greater in women aged 40–49 years when comparing the analyzed data [6–12] with the data of the Breast Cancer Surveillance Consortium (BCSC) [3]. The USPSTF thus recommended against routine screening mammography in women aged 40–49 years (grade C recommendation) [4]. That recommendation, however, has not escaped criticism [5]. That paper reevaluated the data that served as the basis for preparation of the USPSTF guidelines and argued that, for maximization of the survival results, it would be necessary to start screening once annually beginning from the age of 40 years [5].

On the other hand, in Japan, screening mammography, which was endorsed in 2000 for women aged 50 years and over, was expanded to cover women aged 40–49 years in 2004. However, at the time of that endorsement, data regarding the improvement in survival and the harms of screening mammography were not yet available. It will take considerable time to elucidate the improvement in survival, and a conclusion cannot be drawn at this time. Conversely, the harms of the technique can be investigated. Accordingly, the present study was designed to evaluate the harms of breast cancer screening by mammography in Japanese women. We studied the harms of screening mammography using the initial test data collected from five prefectures. The analyzed harms consisted of false-positive results, unnecessary additional imaging tests, and the need for biopsies and their procedures, which were compared with the US data.

Materials and methods

We collected community-based screening mammography data for 144,848 participants that had been recorded in fiscal 2008 in five prefectures—Gunma, Ibaraki, Fukui, Miyagi and Tokushima—with the support of the Japan Association of Breast Cancer Screening. Participants undergo—in principle—biennial screening mammography, based on the guidelines of the Japanese Ministry of Health, Labour and Welfare. Using a questionnaire, we inquired about the following items by age bracket (40–49, 50–59, 60–69, and 70 years or over): the number of participants, number recalled, number of responders and number of detected breast cancer cases. Recalls were defined as women who required further examinations after the initial screening. Responders were defined as women who were recalled after the initial screening because of a positive finding and actually presented for further examination. False-positive screenings were defined as the proportion of recalls except cases whose further examinations proved to be breast cancer.

We ascertained the methods used for additional imaging [mammography, ultrasound (US)] and interventions [cytological examination by fine-needle aspiration cytology (FNA) and histological examination] for women with or without breast cancer by age bracket. We used data from only four of those Japanese prefectures (Gunma, Ibaraki, Fukui and Miyagi) for analysis of the details of the further examinations [additional mammography, additional US, cytological examination by FNA and biopsy (any method)], because the data from Tokushima lacked adequate details.

Furthermore, we ascertained the details of biopsy, such as core-needle biopsy (CNB), vacuum-assisted biopsy

Table 1 Total data of this analysis of all five prefectures

Prefecture	Participants	Recalled		Responders		Cancer		PPV	False positive	
	(*n*)	(*n*)	(%)	(*n*)	(%)	(*n*)	(%)		(*n*)	(%)
Gunma	22,893	1,172	5.1	1,124	95.9	75	0.33	6.4%	1,097	4.8
Ibaraki	63,451	3,451	5.4	3,055	88.5	121	0.19	3.5%	3,330	5.2
Fukui	13,796	1,534	11.1	1,418	92.4	43	0.31	2.8%	1,491	10.8
Miyagi	32,847	3,066	9.3	3,036	99.0	115	0.35	3.8%	2,951	9.0
Tokushima	11,861	1,134	9.6	1,061	93.6	51	0.43	4.5%	1,083	9.1
Total	144,848	10,357	7.2	9,694	93.6	405	0.28	3.9%	9,952	6.9

PPV positive predictive value

(VAB) and open surgical biopsy (OSB), for each age bracket. CNB was defined as percutaneous histological examination using an 11, 14- or 16-gauge needle without aspiration. VAB was defined as percutaneous histological examination using a needle with aspiration by Mammotome® (Johnson & Johnson Ethicon Endo-Surgery, Inc., Cincinnati, OH) and Vacora® (BARD, Murray Hill, NJ, USA). Data from only three prefectures (Gunma, Ibaraki and Fukui) were used for analysis of the details of the histological examination methodology (CNB, VAB or OSB), because the data from Miyagi and Tokushima lacked sufficient detail.

Differences in the recall rate, response rate, cancer yields, positive predictive values, false positives, additional imaging (screening mammography, US), FNA and biopsy between ages 40–49 years and the other age brackets were statistically evaluated using the chi-square test. The Japanese data and BCSC data on the harms were also comparatively analyzed. Differences were regarded as significant if the two-sided P value was <0.05.

Results

Table 1 shows the region-specific data. The data obtained from the five prefectures and the age-specific data are summarized in Table 2. In women aged 40–49 years, the recall rate (9.9%) and false-positive rate (9.6%) were higher than in the other age brackets, with statistical significance ($p < 0.001$). The response rate for detailed examinations (92.2%) and the positive predictive value (2.8%) were slightly lower in the women in their 40s than in women in the other age brackets. Cancer detection rates in the 40s, 50s, 60s and above 70 were 0.28, 0.25, 0.24 and 0.43%, respectively.

Table 3 shows the data for the additional imaging and interventions performed in the four analyzed prefectures. The respective rates of performance of mammography, US, cytological examination (FNA) and biopsy (histological examination) as the detailed investigations were 4.0, 4.8, 0.9 and 0.4% among the total participants, and 5.8%, 7.3%, 1.6% and 0.7% in women aged 40–49 years. The rates of additional imaging, FNA and biopsy were significantly higher in the 40s than in the other age brackets ($p < 0.001$).

Table 4 presents the details of the information obtained by histological examinations (CNB, VAB and OSB) performed in Gunma, Ibaraki, Fukui and Miyagi prefectures. CNB, VAB and OSB were performed in 0.26, 0.08 and 0.04% of the total participants, respectively. Each of those rates was highest for women in their 40s: 0.38, 0.16 and 0.07%. Next, the Japanese and BCSC data on the harms were comparatively analyzed (Table 5) [3]. The harms in terms of false positivity and unnecessary additional

Table 2 Analysis by age bracket (data from all five prefectures)

Age Bracket	Participants	Recalled			Responders			Breast cancer cases (cancer yield)			PPV		False positives		
(years)	(*n*)	(*n*)	(%)	(*p*)	(*n*)	(%)	(*p*)	(*n*)	(%)	(*p*)	(%)	(*p*)	(*n*)	(%)	(*p*)
40–49	33,924	3,357	9.9		3,096	92.2		95	0.28		2.8		3,262	9.6	
50–59	43,144	3,051	7.1	$p < 0.001$	2,836	93.0	$p = 0.267$	107	0.25	$p = 0.388$	3.5	$p = 0.121$	2,944	6.8	$p < 0.001$
60–69	46,650	2,591	5.6	$p < 0.001$	2,461	95.0	$p < 0.001$	113	0.24	$p = 0.296$	4.4	$p < 0.01$	2,478	5.3	$p < 0.001$
70 -	21,130	1,358	6.4	$p < 0.001$	1,301	95.8	$p < 0.001$	90	0.43	$p < 0.05$	6.6	$p < 0.001$	1,268	6.0	$p < 0.001$
Total	144,848	10,357	7.2		9,694	93.6		405	0.28		3.9		9,952	6.9	

PPV positive predictive value

Table 3 Rates of additional imaging and interventions (data from four prefectures)

Age (years)	Participants	Further evaluation of responders											
		Additional MMG			Additional US			FNA			Biopsy[a]		
	(*n*)	(*n*)	(%)[b]	(*p*)	(*n*)	(%)[b]	(*p*)	(*n*)	(%)[b]	(*p*)	(*n*)	(%)[b]	(*p*)
40–49	31,323	1,813	5.8		2,298	7.3		503	1.6		215	0.7	
50–59	40,199	1,728	4.3	$p < 0.001$	2,003	5.0	$p < 0.001$	359	0.9	$p < 0.001$	160	0.4	$p < 0.001$
60–69	42,789	1,304	3.0	$p < 0.001$	1,521	3.6	$p < 0.001$	204	0.5	$p < 0.001$	105	0.2	$p < 0.001$
70–	18,676	522	2.8	$p < 0.001$	586	3.1	$p < 0.001$	83	0.4	$p < 0.001$	78	0.4	$p < 0.001$
Total	132,987	5,367	4.0		6,408	4.8		1,149	0.9		558	0.4	

MMG Mammography, *US* ultrasound, *FNA* fine-needle aspiration cytology

[a] Number of cases undergoing histological examination

[b] % of participants

Table 4 Rates of each type of biopsy (data from three prefectures)

Age (years)	Participants	Type of biopsy								
		CNB			VAB			OSB		
	(*n*)	(*n*)	(%)[a]	(*p*)	(*n*)	(%)[a]	(*p*)	(*n*)	(%)[a]	(*p*)
40–49	25,159	95	0.38		39	0.16		17	0.07	
50–59	30,526	80	0.26	$p < 0.05$	26	0.09	$p < 0.05$	13	0.04	$p = 0.206$
60–69	32,491	49	0.15	$p < 0.001$	12	0.04	$p < 0.001$	9	0.03	$p < 0.05$
70–	11,964	34	0.28	$p = 0.153$	4	0.03	$p < 0.001$	4	0.03	$p = 0.196$
Total	100,140	258	0.26		81	0.08		43	0.04	

CNB Core-needle biopsy, *VAB* vacuum-assisted biopsy, *OSB* open surgical biopsy

[a] % of participants

imaging and biopsy were greatest for women in their 40s in Japan, but less than in the BCSC in all age brackets. In addition, the cancer detection rate per 1,000 screened in Japanese women aged 40–49 years was 2.8, which was slightly higher than the 2.6 recorded in the BCSC data.

Discussion

The USPSTF recommended against routine screening mammography in women aged 40–49 years [4]. As background to that recommendation, in terms of the benefit, screening mammography in the 40s results in 15% mortality reduction, and it was acknowledged to have a benefit in eight RCT meta-analyses. However, in terms of the harms, the BCSC data indicated that they (especially false positivity, unnecessary additional imaging and biopsy) were relatively greater for women in their 40s [4].

In this study, as well, the harms in terms of false positivity and performance of unnecessary additional imaging and biopsy were greatest for Japanese women in their 40s, but less than in the BCSC in all age brackets. Thus, screening mammography appears to be less harmful in Japan than in the US. In a report from the US [13], the relative proportions of biopsy performed using CNB, VAB and OSB were 23.2, 40.0 and 36.8% for women as a whole, and 25.3, 40.4 and 34.2% for women aged 40–49 years, respectively. That study found that the proportion of OSB has declined by the year, but it remains at approximately 30%. Figure 1 illustrates, per 1,000 screened women in their 40s, the estimated numbers of additional imaging, FNA, biopsy and its procedures, false positives and detected cancers. The number of biopsy procedures was calculated from the data for three prefectures in Japan and from the data of the US report [13]. As biopsy procedures, the respective numbers of CNB, VAB and OSB are approximately 3.8, 1.6 and 0.7 per 1,000 screened women in Japan, and 2.4, 3.8 and 3.2 in the US. These data suggest that once US women in their 40s go for screening, they undergo more biopsies and OSBs than in Japan. Based on these results, in addition to the lower rates of false positives, additional imaging and biopsy, the invasiveness of biopsy is lower in Japan. Accordingly, we speculate that the harms of breast cancer screening in women in their 40s are less in Japan than in the US. The costs associated with CNB, VAB and OSB in Japan are 19,300, 55,800 and

Table 5 Comparison of the data from the BCSC and this study

	Source	Age bracket (years)			
		40–49	50–59	60–69	70–
Outcomes per screening round (per 1,000 screened)					
False-positive mammogram	BCSC[a]	97.8	86.6	79.0	68.8
	This study[b]	96.2	68.2	53.1	60.1
Additional imaging	BCSC[a]	84.3	75.9	70.2	64.0
	This study[c]	73.4	49.8	35.5	31.4
Biopsy	BCSC[a]	9.3	10.8	11.6	12.2
	This study[c]	6.9	4.0	2.5	4.2
Screening-detected breast cancer[d]	BCSC[a]	2.6	4.7	6.5	7.9
	This study[b]	2.8	2.5	2.4	4.3

[a] Data from BCSC (Breast Cancer Surveillance Consortium) were cited from Ref. [3]

[b] Calculated from Table 2

[c] Calculated from Table 3

[d] Including invasive cancer and DCIS

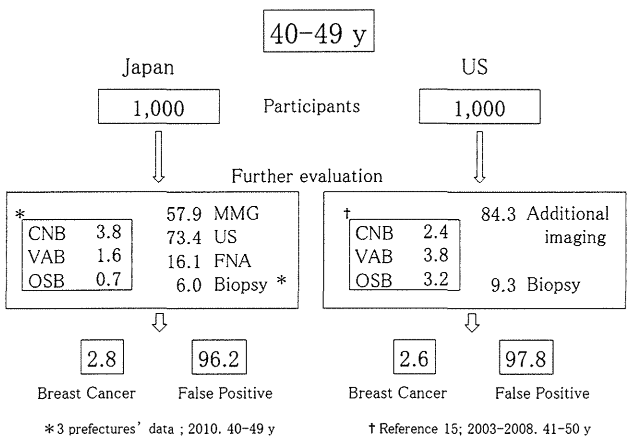

Fig. 1 The estimated numbers of additional imaging, FNA, biopsy and its procedures, false positives and detected cancers per 1,000 screened women in their 40s

65,600 Yen (including the pathological diagnosis fee), respectively, which are only 1/8 to 1/18 of the costs in the US [13]. We need to evaluate the harms of screening in consideration of the different economic circumstances between the countries. The benefit of screening can be assessed by a single measure of the decrease in mortality. With regard to its harms, however, the weight of each criterion differs by country, region, economic status and personal values. An overall net benefit should be decided upon, accounting for all the above factors.

One of the limitations of this study was that our data were taken from only 5 of the 47 prefectures in Japan. The participating prefectures had been conducting breast cancer screening for a long period, and their data can be assumed to be relatively accurate. However, analysis of larger data sets for the whole nation will be necessary before any firm conclusions can be drawn about the net benefit of breast cancer screening for Japanese women. A second limitation is that we did not focus on the other harms of breast cancer screening, such as psychological harm, over-diagnosis, radiation exposure and false-negative results. Psychological harm is said to be transient [14]. Over-diagnosis tends to occur mainly in older women, and methods for calculating it are not well established. Radiation exposure resulting from screening mammography might itself cause breast cancer, but the risk appears negligible [3].

We conclude that the major harms, consisting of false-positive results, unnecessary additional imaging, and the need for biopsy and its invasiveness, are greatest in women in their 40s undergoing breast cancer screening mammography in Japan, but they seemed to be less than those reported by the BCSC and other studies in the US. In the future, it will be necessary to compile more data regarding the mortality reduction and the accompanying harms in order to prove the efficacy of screening mammography in Japanese women age 40–49 years.

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Retrospective analysis of mammographic findings for Japanese women: A potential predictor for breast malignancies

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This purpose of this study was to retrospectively stratify the risks of malignancy according to the mammographic characteristics of Japanese women. We studied the mammographic findings of 1267 Japanese women. We characterized malignant phenotypes according to mass shape, margin and mass density, and by shape and distribution of calcified foci, and to obtain possible predictors for malignancies according to age groups. Lobular and irregular mass shape, no circumscribed margin and higher density turned out to be more powerful predictors for malignancy than other radiological factors (P < 0.001, respectively). The ratio of the cases detected as a mass in those between 21 and 49 years was lower than that of other age groups. In addition, the presence of calcifications and no mammographic abnormalities were the most powerful predictors for malignancies in the young age groups (P < 0.001, respectively). The peak age of breast cancer is between 40 and 49 years in Japan. In the present study, subtle differences were found in the mammographic results for young and old women, in contrast to those of women in the USA and Europe. The results of this study might enable more accurate prediction of biological behavior of the breast lesions in Japanese women. (*Cancer Sci*, doi: 10.1111/j.1349-7006.2011.02169.x, 2011)

The incidence of breast cancer continues to increase worldwide.[(1)] Morbidity and death due to breast cancer are lower in Japan than in the USA and Europe, but their rates have been markedly increased in this decade.[(2)] The effectiveness of screening mammography in reducing death from breast cancer has been established in both the USA, Europe and Japan.[(3)] Worldwide, millions of mammographic examinations are performed each year, and mammography has become the gold standard for detecting breast disorders. It is important to continue to increase the mammographic screening ratio in order to reduce breast cancer deaths.

The American College of Radiology (ACR) has developed the Breast Imaging Reporting and Data System (BI-RADS) to standardize mammographic reporting, to improve communication with clinicians, to reduce confusion regarding mammographic findings, to aid research and to facilitate outcomes monitoring.[(4)] The use of BI-RADS lexicon is increasing not only in the North American continent but also worldwide.[(5)] However, some publications have raised the issue of observer variability of interpretation of the lexicon, and have even questioned the expressiveness of the BI-RADS system.[(6,7)] Some published studies propose classifications of features for the assignment of findings to the various BI-RADS categories.[(6,7)]

Some published reports suggest possible differences in the biological characteristics of breast cancer between women in the USA and Europe and Japanese women.[(8)] A striking difference is that the peak age for breast cancer is between 40 and 50 years in Japan, whereas the peak age in the USA and Europe is between 60 and 70 years.[(8)] We have observed that the mammographic findings for Japanese women do not exactly correspond to those defined in BI-RADS lexicon. The dense parenchyma in women before menopause can obscure tumor shadows, which results in the lower sensitivity of mammography screening in women 40–49 years of age.[(9)] The purpose of the present study was to retrospectively stratify the risk of malignancy according to mammographic characteristics of Japanese women.

Materials and Methods

Patients. This is a retrospective study. We examined mammographical findings of 1267 Japanese women (707 malignant and 560 benign breast diseases) who underwent needle biopsies or surgical resection at the Tohoku University Hospital. We received informed consent from all patients and the protocol for this study was approved by the Ethics Committee at Tohoku University Graduate School of Medicine. The median age of the patients was 52 years (range, 21–89 years). The numbers of biopsy or surgical resection cases were: 151 for 21–39 years, 393 for 40–49 years, 355 for 50–59 years, 215 for 60–69 years and 153 for 70–89 years. The numbers of malignant cases were: 56 for 20–39 years, 205 for 40–49 years, 175 for 50–59 years, 147 for 60–69 years and 124 for 70–89 years. The criteria for performing a biopsy were BI-RADS assessment categories of mammography and ultrasound category 4 or more.

Imaging and evaluation. All mammographic examinations were performed with dedicated machines. Analog mammographic examinations were performed with one unit (MAMMOMAT 3000 Nova; Siemens AG, Erlangen, Germany) and using a screen-film technique (Min-R 2000 Min-R EV; Kodak Health Imaging, Rochester, NY, USA). Digital mammograms were acquired using a system with an amorphous selenium DirectRay digital detector (LOARD Selenia; Hologic, Waltham, MA, USA). The system was connected to a viewing monitor (MammoRead; TOYO Corporation, Tokyo, Japan).

We first examined the correlation between mammographic findings and the ratio of malignant cases. Two of the authors independently evaluated mammographic findings. These two investigators were blinded to the clinical outcome of the patients. The presence of mass, calcification and the other findings, including architectural distortion, focal asymmetric density and asymmetric breast tissue (ABT) were each recorded. As for mass, shape was tentatively classified as round, oval, lobular or irregular. Margin was classified as circumscribed, microlobulated, indistinct or spiculated. Density was classified into higher,

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equivalent or lower. Shape of calcification was tentatively classified as punctuate, amorphous, pleomorphic or linear. Distribution was classified as diffuse, grouped or segmental. We classified FAD and ABT into those with or without architectural distortion. We first examined the correlation between mammographic findings and the ratio of malignant cases. We then examined the ratio of malignant cases according to mammographic findings. We devised classification system for predicting. In addition, we attempted to obtain possible predictors for malignancies according to age groups: 21–39, 40–49, 50–59, 60–69 and 70–89 years. If there were two or more findings in a mammography, we determined the priority for mammographic findings as follows: mass, calcification, other findings including architectural distortion, FAD and ABT, and no mammographic abnormality, and recorded a prior finding as a possible predictor for malignancy.

Statistical analysis. Statistical analyses were performed using StatMate IV for Windows (ATMS, Tokyo, Japan). Results were considered significant at $P < 0.05$.

Results

Sensitivity, specificity and PPV by age groups. Of the 1040 cases with mammographic findings, 656 were malignant and 384 were benign, whereas 51 of the 227 cases without any mammographic findings were malignant. Sensitivity, specificity and positive predictive value were 92.8, 31.4 and 63.1%, respectively. In addition, sensitivity, specificity and PPV by age groups were: 87.5, 40.0 and 46.2% for 21–39 years; 86.8, 35.2 and 51.5% for 40–49 years; 96.1, 29.3 and 66.6% for 50–59 years, 96.6%, 17.6 and 71.7% for 60–69 years; and 93.5, 31.0 and 85.3% for 70–89 years, respectively.

Correlation between mammographic findings and ratio of malignant cases. The ratio of malignant cases according to the mass shape were 46.7% (28/60) of round, 45.1% (23/51) of oval, 83.3% (62/74) of lobular and 94.9% (131/138) of irregular lesions, respectively (Fig. 1A). There were statistically significant differences between round or oval and lobular or irregular shape ($P < 0.001$, respectively). The ratio of malignant cases according to the margin were 19.3% (11/57) of circumscribed, 75.5% (74/98) of microlobulated, 87.3% (62/71) of indistinct and 100% (97/97) of spiculated margin, respectively (Fig. 1B). There were statistically significant differences between circumscribed and the other characteristics, and microlobulated and spiculated margin ($P < 0.001$, respectively). The ratios of malignant cases according to mass density were 81.7% (210/257) of higher, 55.9% (33/59) of equivalent and 14.3% (1/7) of lower mass density, respectively (Fig. 1C). There were statistically significant differences between higher and equivalent or lower mass density ($P < 0.001$). The ratios of malignant cases according to calcification type were 28.1% (25/89) of punctuate, 48.3% (129/267) of amorphous, 88.4% (137/155) of pleomorphic and 100% (20/20) of linear type, respectively (Fig. 2A). There were statistically significant differences between punctuate or amorphous and any calcification shapes ($P = 0.001$ for between punctuate and amorphous, $P < 0.001$ for the other combinations). The ratios of malignant cases according to distribution of calcification were 16.7% (1/6) of diffuse, 53.1% (146/275) of grouped and 65.6% (164/250) of segmental (Fig. 2B). There were statistically significant differences between segmental and diffuse or grouped cases ($P = 0.041$ and $P = 0.005$, respectively).

Classifications for predicting malignancies. We attempted to devise a classification system predicting malignancies (Table 1). The masses with spiculated or microlobulated margins, and the masses with lobular or irregular mass shapes and indistinct margins turned out to be more powerful predictors of malignancies than the other radiological factors ($P < 0.001$). In contrast, the masses with circumscribed margins and equivalent or lower mass densities were less powerful predictors of malignancies ($P = 0.154$).

Mammographic findings of all the cases by age groups. Mammographic findings of all cases by age group are summarized in Figure 3A. The ratios of the cases detected as a mass were 18.5% for 21–39 years, 16.8% for 40–49 years, 25.4% for 50–59 years, 31.6% for 60–69 years and 46.4% for 70–89 years, respectively. There were statistically significant differences between 21 and 39 and 60–69 ($P = 0.007$) or 70–89 years ($P < 0.001$), 40–49 and 50–59 years ($P = 0.005$), 60–69 ($P < 0.001$) or 70–89 years ($P < 0.001$), 50–59 and 70–89 years ($P < 0.001$), and 60–69 and 70–89 years ($P = 0.006$). The ratios of calcification were 29.8% for 21–39 years, 41.7% for 40–49 years, 41.4% for 50–59 years, 39.5% for 60–69 years and 24.8% for 70–89 years, respectively. There were statistically significant differences between 20 and 39 and 40–49 ($P = 0.014$) or 50–59 years ($P = 0.021$), 40–49 and 70–89 years ($P < 0.001$), 50–59 and 70–89 years ($P < 0.001$), and 60–69 and 70–89 years ($P = 0.005$). The ratios of the other findings, including architectural distortion, FAD and ABT were 21.9% for 21–39 years, 16.3% for 40–49 years, 19.7% for 50–59 years, 20.9% for 60–69 years and 17.6% for 70–89 years, respectively. There were no statistically significant differences

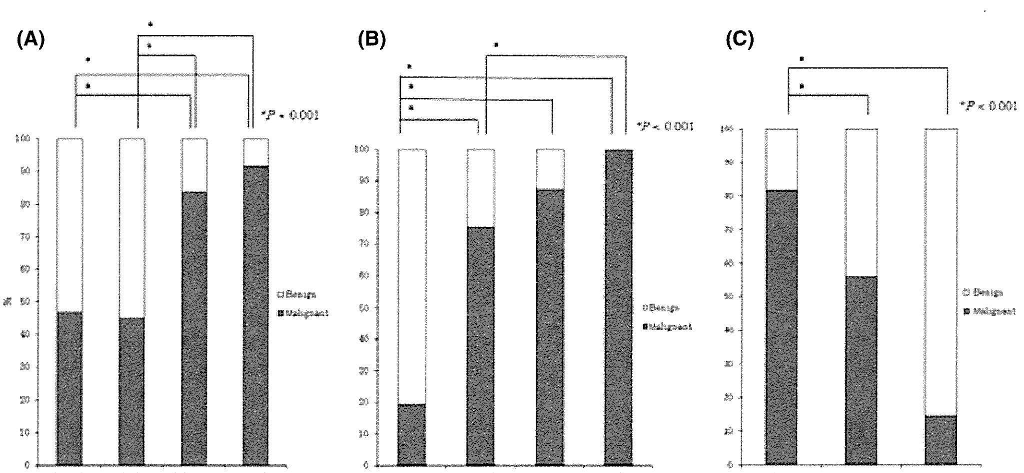

Fig. 1. Correlation between mammographic findings of masses and malignant ratio: (A) mass shape, (B) margin and (C) mass density.

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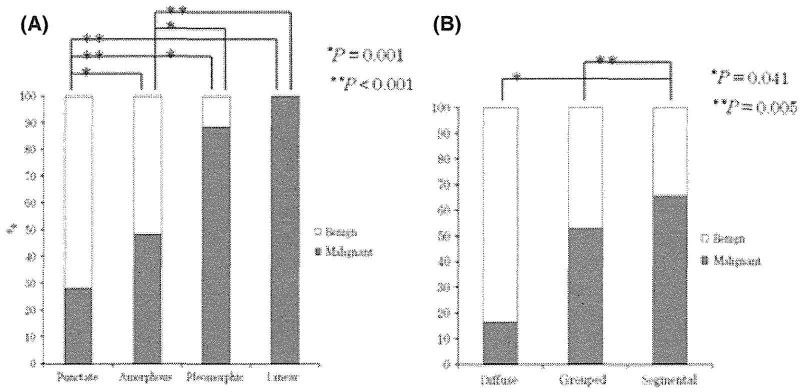

Fig. 2. Correlation between mammographic findings of calcifications and malignant ratio: (A) characteristics of calcification and (B) distribution.

Table 1. Classifications for predicting malignancies

	Malignant ratio (%)	Mammographic findings		Total number	No. malignancies	Ratio of malignant cases (%)	*P*-value	Odds ratio
Class I	0–20	Mass	Any mass shape-circumscribed-equivalent or lower	25	2	8.0	0.154	0.30
		Calcification	Punctate-diffuse or grouped	42	7	16.7	0.525	0.69
Class II	20–40	Mass	Round-circumscribed-higher-with calcification	19	5	26.3	0.921	1.23
			Oval-circumscribed-higher	12	3	25.0	0.881	1.15
			Oval-microlobulated-equivalent	8	3	37.5	0.572	2.07
		Calcification	Punctate-segmental	28	6	21.4	0.907	0.94
			Amorphous-diffuse or grouped	106	30	28.3	0.308	1.36
Class III	40–60	Mass	Round-indistinct-higher	4	2	50.0	0.485	3.45
			Lobular-microlobulated or indistinct-equivalent	6	3	50.0	0.277	3.45
		Calcification	Punctate-grouped-with FAD	9	5	55.6	0.589	4.31
			Amorphous-segmental	86	37	43.0	<0.001	2.61
		FAD	Without distortion	123	50	40.7	<0.001	2.36
Class IV	60–80	Mass	Irregular, round or lobular-microlobulated-higher	62	46	74.2	<0.001	9.92
		Calcification	Punctate-segmental-with FAD	6	4	66.7	0.420	6.90
			Amorphous-grouped or segmental-with FAD	53	41	77.4	<0.001	11.79
			Pleomorphic-grouped	43	33	76.7	<0.001	11.39
		ABT	Without distortion	5	4	80.0	0.014	13.80
Class V	80–100	Mass	Any mass shape-spiculated-any density	100	100	100.0	<0.001	–
			Any mass shape-microlobulated-any density-with calcification	18	17	94.4	<0.001	58.67
			Lobular or irregular-obscured or indistinct-any findings	64	58	90.6	<0.001	33.36
		Calcification	Pleomorphic-grouped or segmental with FAD	32	29	90.6	<0.001	33.36
			Pleomorphic-segmental	58	53	91.4	<0.001	36.58
			Linear-any distribution	16	16	100.0	<0.001	–
		FAD	With distortion	90	77	85.6	<0.001	20.44
		ABT	With distortion	20	20	100.0	<0.001	–

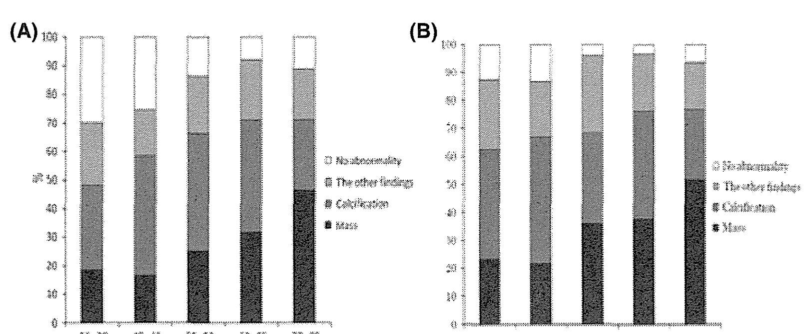

Fig. 3. The ratio of mammographic findings by age groups: (A) mammographic findings of all cases by age groups and (B) mammographic findings of malignant cases by age groups.

among age groups. The ratios of the cases without mammographic abnormalities were 29.8% for 21–39 years, 25.4% for 40–49 years, 13.8% for 50–59 years, 7.9% for 60–69 years and 11.1% for 70–89 years, respectively. There were statistically significant differences between 21 and 39 and 50–59 ($P < 0.001$), 60–69 ($P < 0.001$) or 70–89 years years ($P < 0.001$), 40–49 and 50–59 ($P < 0.001$), 60–69 ($P < 0.001$) or 70–89 years ($P < 0.001$), and 50–59 and 60–69 years ($P = 0.046$).

Mammographic findings of malignant cases by age groups. Mammographic findings of malignant cases by age group are summarized in Figure 3B. The ratios of the cases detected as a mass were 23.2% for 21–39 years, 21.7% for 40–49 years, 36.1% for 50–59 years, 37.4% for 60–69 years and 51.6% for 70–89 years, respectively. There were statistically significant differences between 21 and 39 and 70–89 years ($P < 0.001$), 40–49 and 50–59 ($P = 0.003$), 60–69 ($P = 0.003$) or 70–89 years ($P < 0.001$), 50–59 and 70–89 years ($P = 0.008$), and 60–69 and 70–89 years ($P = 0.026$). The ratios of calcification were 39.3% for 21–39 years, 45.1% for 40–49 years, 35.1% for 50–59 years, 38.8% for 60–69 years and 25.0% for 70–89 years, respectively. The only statistically significant differences ware between 40 and 49 and 70–89 years ($P < 0.001$). The ratios of the other findings including architectural distortion, FAD and ABT were 25.0% for 21–39 years, 19.4% for 40–49 years, 24.9% for 50–59 years, 20.4% for 60–69 years and 22.1% for 70–89 years. There were statistically significant differences between 50 and 59 and 70–89 years ($P = 0.046$). The ratios of the cases without mammographic abnormalities were 12.5% for 21–39 years, 13.1% for 40–49 years, 3.9% for 50–59 years, 3.4% for 60–69 years and 6.5% for 70–89 years, respectively. There were statistically significant differences between 21 and 39 and 50–59 ($P = 0.034$) or 60–69 years ($P = 0.034$), and 40–49 and 50–59 ($P = 0.002$) or 60–69 years ($P = 0.004$).

Mammographic predictors for malignancy by age groups. The distinctive mammographic predictors for malignancy by age group are summarized in Table 2. The masses not only spiculated but also with microlobulated and indistinct margins turned out to be powerful predictors for malignancies in the groups of 50–59 years and above (Table 2).

Discussion

The BI-RADS lexicon was created and has evolved to help capture predictive mammographic descriptors in a standardized manner in the USA and Europe.[4,10] Various biological features of breast cancer have been found to be different between women in the USA and Europe and Japanese women.[8,11] Mammographic findings of Japanese women do not exactly correspond to those defined in BI-RADS lexicon for women in the USA and Europe.

The results of this study demonstrate that lobular and irregular mass shape, no circumscribed margin and higher density are more powerful predictors of malignancy than the other findings with statistical significance. As for calcification, a statistically significant difference was detected between necrotic and secretary calcification. FAD combined with architectural distortion represented a high malignant ratio of up to 80%. These results were similar to those in the BI-RADS lexicon.

Table 2. Mammographic predictors for malignancy by age groups

Years	Mammographic findings		Total number	No. malignancies	Ratio of malignant cases (%)	*P*-value	Odds ratio
21–39	Mass	Irregular-spiculated: with calcification	4	4	100.0	0.001	–
	Calcification	Amorphous-segmental-with FAD	4	4	100.0	0.001	–
		Pleomorphic-any distribution	11	9	81.8	<0.001	15.53
	FAD	With distortion	11	8	72.7	<0.001	14.1
40–49	Mass	Lobular-indistinct or spiculated-high	5	5	100.0	0.001	–
		Irregular-indistinct-high	10	8	80.0	<0.001	13.8
		Irregular-spiculated-any density	13	13	100.0	<0.001	–
	Calcification	Amorphous-segmental	52	26	50.0	0.001	3.35
		Pleomorphic-any distribution	37	35	94.6	<0.001	58.59
		Linear-segmental	4	4	100.0	0.004	–
	FAD	With distortion	23	19	82.6	<0.001	15.9
	ABT	With distortion	4	4	100.0	0.004	–
50–59	Mass	Round-indistinct or microlobulated-equivalent or high	6	6	100.0	<0.001	–
		Oval-microlobulated-high	8	6	75.0	0.002	15.35
		Lobular-indistinct or microlobulated-high	14	13	92.9	<0.001	44.86
		Irregular-indistinct, obscured or spiculated	43	43	100.0	<0.001	–
	Calcification	Amorphous-grouped-with FAD	8	8	100.0	<0.001	–
		Amorphous-segmental	27	14	51.9	0.002	3.72
		Pleomorphic-any distribution	43	33	76.7	<0.001	11.39
	FAD	With or without distortion	63	44	69.8	<0.001	7.99
	ABT	With distortion	7	7	100.0	<0.001	–
60–69	Mass	Round-circumscribed or microlobulated-high	6	6	100.0	0.012	–
		Lobular-microlobulated or indistinct-any density	11	10	90.9	<0.001	34.51
		Irregular-any periphery-any density	31	31	100.0	<0.001	–
	Calcification	Amorphous-segmental-with FAD	5	5	100.0	0.025	–
		Pleomorphic-any distribution	28	26	92.9	<0.001	31.2
		Linear-any distribution	5	5	100.0	0.045	–
	FAD	With distortion	19	17	89.5	<0.001	20.4
	ABT	With or without distortion	4	4	100.0	0.045	–
70–89	Mass	Lobular or irregular, any periphery, any density	52	49	94.2	<0.001	56.37
	Calcification	Pleomorphic, any distribution	14	13	92.9	0.013	16.25

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However, the striking difference between Japanese and the USA and Europe breast cancer patients is that the peak age for breast cancer was between 40 and 50 years in the Japan, whereas the peak age in the USA and Europe was between 60 and 70 years.[8] The results of our present study reveals that the peak age of breast cancer was 40 years. There were subtle differences in mammographic findings between young and old women, which are different from those of women in the USA and Europe. Previous studies have demonstrated that mass is the more powerful predictor in women in the USA and Europe.[12,13] However, the results in the present study demonstrate that the ratio of the cases detected as a mass between 21 and 49 years was lower than that of the other age groups. In addition, the masses that were spiculated and had microlobulated and indistinct margins turned out to be powerful predictors for malignancies in those of 50 years and above, whereas only limited masses were predictors for those under 49 years old. Therefore, the presence of a mammographic mass is not necessarily the most powerful predictor for malignancy in Japanese women.

The results of the present study also demonstrated that 7.2% (51/707) of malignant cases had mammographic abnormalities. In addition, the ratios of malignant cases in those of 20, 30 and 40 years without mammographic abnormalities were statistically higher than the ratios of the other age groups. There was dense parenchyma in women before menopause. A previous study demonstrated that the percentage of extremely dense and dense breast were 76.3% of 40 years, 51.5% of 50 years and 17.6% of 60 years in Japanese breast cancer cases, respectively.[9] Breast masses are indicated by their density in the mammography. In addition, the mass findings are often hidden in a dense breast. Previous study has demonstrated that screening mammography is effective for women aged 50 years and over to detect malignancy, whereas the effectiveness for women under 50 years has not been proven.[3] Ohuchi *et al.*[14] suggested that screening mammography alone for Japanese women aged 40 years and over is insufficient. For the purpose of complementing this weakness of mammography, the effectiveness of ultrasound screening for women aged 40 years and over has been evaluated in relation to detecting and reducing death as a result of breast cancer in Japan.[14]

In the present study, we attempted to establish mammographic criteria for Japanese women for predicting breast malignancy. We examined the mammographic characteristics according to age groups. Lobular and irregular mass shape, no circumscribed margin and higher density turned out to be more powerful predictors for malignancy than other radiological factors. In addition, the ratio of the cases detected as a mass between 21 and 49 years was lower than that for other age groups. The presence of calcifications and no mammographic abnormalities was one of the most powerful predictors for malignancies in the young age groups. However, this study was retrospective and took place in a single institute. Therefore, it is probable that further investigation not only with Japanese women but also with other Asian women will confirm the new mammographic criteria. The results of this study might enable more accurate prediction of the biological behavior of the breast lesions in Japanese women.

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Disclosure Statement

The authors have no conflict of interest.

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Correlation between mammographic findings and corresponding histopathology: Potential predictors for biological characteristics of breast diseases

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The present study retrospectively evaluated the mammographic findings of 606 Japanese women with breast cancer (median age 50 years; range 27–89 years) and correlated them with histopathological characteristics. Mammographic findings were evaluated with an emphasis on mass shape, margin, density, calcification, and the presence of architectural distortion; these findings were correlated with histopathological characteristics such as intrinsic subtype, histological grade, lymphovascular invasion, and the Ki-67 labeling index. An irregular mass shape and masses with a spiculated margin were significantly higher in the group of patients with luminal A breast cancer than in patients with masses that were lobular or round, or in tumors with an indistinct or microlobulated periphery ($P = 0.017$, $P = 0.024$, $P < 0.001$, and $P = 0.001$, respectively). Irregular mass shape and spiculated periphery were significantly lower in patients with Grade 3 cancer ($P < 0.001$ for both). In terms of lymphovascular invasion, there were significant differences between oval and irregular or round mass shape ($P = 0.008$ and $P = 0.034$), between tumors with a microlobulated and indistinct periphery ($P = 0.014$), between tumors with a punctate and amorphous or pleomorphic calcification shape ($P = 0.030$ and 0.038), and between the presence and absence of architectural distortion ($P = 0.027$). Equivalent or low-density masses were also higher in Grade 1 breast cancers ($P = 0.007$). There were significant differences in the Ki-67 labeling index between irregular and lobular or round tumors ($P < 0.001$ and $P = 0.014$), as well as between spiculated and indistinct or microlobulated tumors ($P < 0.001$ for both). Significant differences were noted in the mammographic features of different primary breast cancer subtypes. These proposed mammographic diagnostic criteria based on biological characteristics may contribute to a more accurate prediction of biological behavior of breast malignancies. (*Cancer Sci* 2011; 102: 2179–2185)

The incidence of breast cancer has increased worldwide, which is considered due, in part, to mass screening programs resulting in the discovery of clinically occult breast lesions. Mammographic screening has been demonstrated to reduce breast cancer mortality in both Western and Oriental populations.(1) This mortality may be as great as 63% in women attending for screening.(2) Therefore, million of mammographic examinations are being performed yearly worldwide, and mammography has become the gold standard for detecting breast disorders. Strict attention to high-quality interpretation is required for successful of a mammographic diagnosis. Thus, it is important to establish an accurate diagnostic system for mammography.

Traditionally, prognostic determinations are made mainly on the basis of pathological information, including histological grade and lymphovascular invasion.(3–5) In addition to histological information, the status of molecular markers that have prognostic and predictive value can contribute to the selection of an optimal treatment strategy. These markers include estrogen receptor (ER), progesterone receptor (PgR), and human epidermal growth factor receptor 2 (HER2) and determining the status of these markers has become standard practice in the management of breast cancer because ER and HER2 positivity can predict a patient's response to endocrine therapy or targeted therapy with monoclonal antibodies directed against HER2.(6) In addition, the St Gallen international expert consensus meeting on the primary treatment of early breast cancer reported that features indicative of increased risk of recurrence, thus indirectly supporting the addition of chemotherapy to endocrine therapy, include lower expression of steroid hormone receptors, Grade 3 tumors, high proliferation (as measured by conventional or multigene assays), and extensive peritumoral vascular invasion.(7) However, these therapeutic determinations have been derived mainly from pathological information.

The appearance of tumors on mammograms has a generally good correlation with subsequent histological characteristics. For example, microcalcification is the hallmark of ductal carcinoma *in situ*;(8) spiculation is significantly correlated with low histologic grade; and ill-defined masses and microcalcifications are features of high-grade tumors.(8) Accurate correlation of mammographic findings with corresponding histopathologic features is considered one of the most important aspects of mammographic evaluation. Full histopathological information, including histological grades and intrinsic subtypes, is determined correctly after surgery.(9) Therefore, the purpose of the present study was to retrospectively evaluate mammographic findings and to compare the histopathological characteristics of the different tumors (i.e. intrinsic subtype, histological grade, lymphovascular invasion, and Ki-67 labeling index) in Japanese patients.

Materials and Methods

Patients. The mammographic and histopathologic features of 606 Japanese breast cancer patients who had undergone surgery at Tohoku University Hospital, Sendai, between January 2005 and June 2010 were reviewed retrospectively. All patients provided informed consent and the study protocol was approved by the Ethics Committee at Tohoku University Graduate School of Medicine. The median age of the patients was 50 years (range 27–89 years).

Imaging devices and breast tissue specimens. All mammographic examinations were performed with dedicated machines.

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Analog mammographic examinations were performed with one unit (MAMMOMAT 3000 Nova; Siemens, Erlangen, Germany) using a screen–film technique (Min-R 2000 Min-R EV; Kodak Health Imaging, Rochester, NY, USA). Digital mammograms were acquired by using a system with an amorphous selenium DirectRay digital detector (LOARD Selenia; Hologic, Waltham, MA, USA). The system was connected to a viewing monitor (MammoRead; TOYO, Tokyo, Japan).

Samples were stained using H&E. Histochemical and immunohistochemical analyses for ER, HER2, and Ki-67 were performed at the Department of Pathology, Tohoku University Hospital. Surgical specimens were fixed in 10% formaldehyde solution and cut into serial 5-mm slices, embedded in paraffin, cut into 4-μm sections, and placed on the glue-coated glass slides. We used the avidin–streptavidin immunoperoxidase method using the clone 6F11 antibody (Ventana, Tucson, AZ, USA) in an automated immunostainer (Benchmark System; Ventana). A standardized immunohistochemistry kit (HercepTest for Immunoenzymatic Staining; Dako, Copenhagen, Denmark) was used for HER2 staining. The Ki-67 labeling index was determined using an MIB-1 monoclonal antibody (code M7240; Dako). Both H&E and immunohistochemical staining were performed by a single experienced technician. Positive controls for ER and HER2 were breast carcinoma, whereas negative controls for immunostaining were hepatocellular carcinoma.

Imaging and histopathological analyses. Two experienced breast surgeons independently evaluated the mammographic findings. These two investigators were blinded as to the histopathological diagnosis and the clinical outcome of the patients. If there were discrepancies in the interpretation of the mammograms, a final decision was reached using consensus evaluations from eight experienced breast surgeons and radiologists. Mammographic findings were subsequently analyzed according to the American College of Radiology Breast Imaging Reporting and Data System (BI-RADS).[10] The presence of a mass, calcifications, focal asymmetric density (FAD), and architectural distortion were each recorded. Figure 1 shows representative mammographic findings. Mass shape was tentatively classified into round, oval, lobular, and irregular. Margins were classified as microlobulated, indistinct, spiculated, and ''other''. Density was classified into high, equivalent, or low. Calcification shape was tentatively classified into punctate, amorphous, pleomorphic, and linear. Finally, FAD was classified as with or without architectural distortion.

Two experienced pathologists independently evaluated surgical specimens. Histopathological evaluations were based on the World Health Organization (WHO) histological classification of tumors of breast and Rosen's Breast Pathology.[11,12] The presence of ER was determined by nuclear staining and was graded from 0 to 8 using the Allred score, with positivity defined as a score of ≥3.[13] With regard to HER2 evaluation, membranous staining was graded as 0–1+, 2+, and 3+.[14] Samples scored as 2+ were subjected to FISH to calculate the gene copy ratio of *HER2* to *CEP17* (PathVysion HER2 DNA Probe kit; Abbott, Chicago, IL, USA). Positivity was defined as a *HER2*:*CEP17*

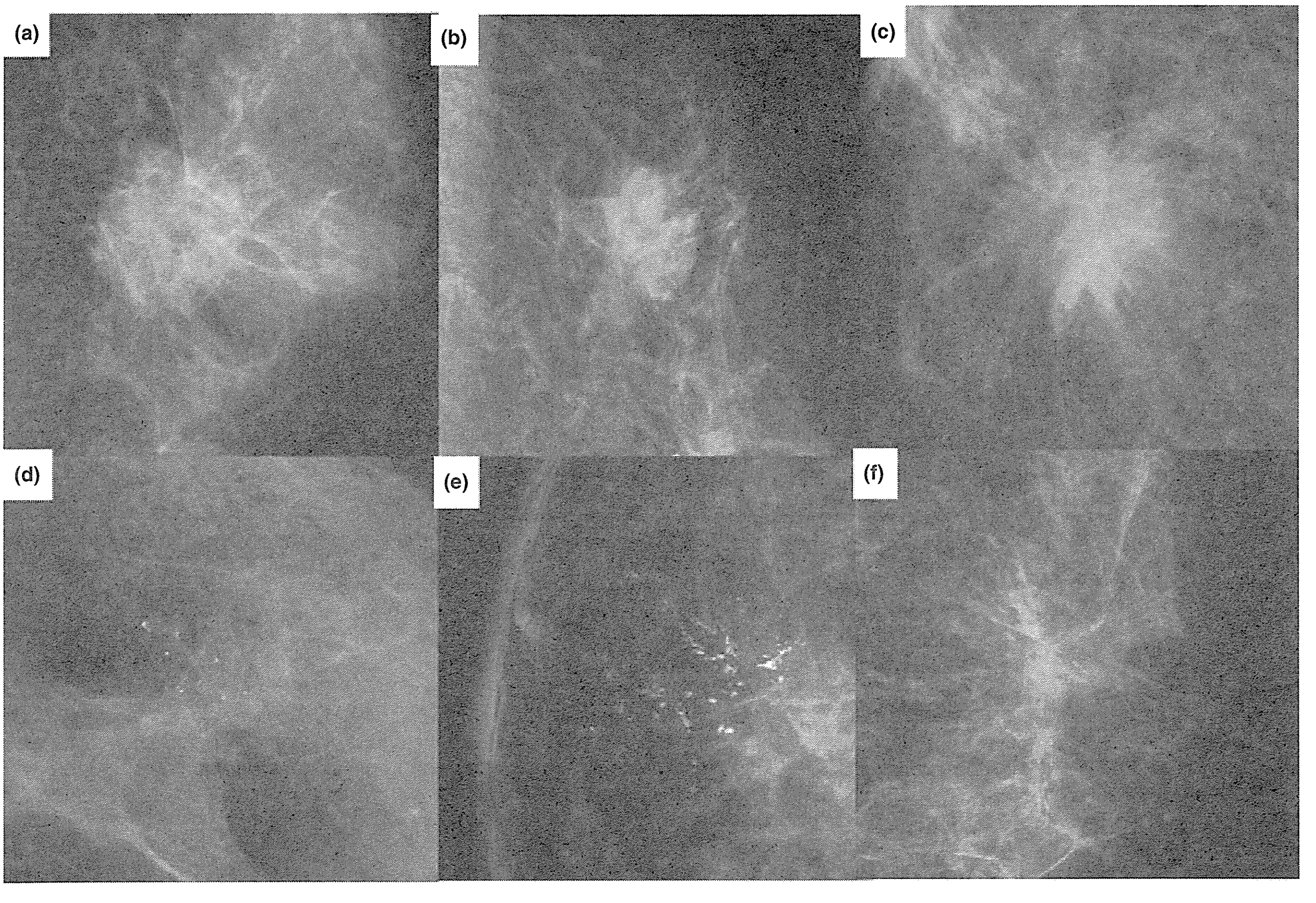

Fig. 1. Representative mammographic findings in breast carcinoma cases. (a) Round mass shape, microlobulated margin and intermediate density mass. (b) Lobular mass shape, indistinct margin, and high density mass. (c) Irregular mass shape, spiculated margin, and high-density mass. (d) Amorphous calcifications. (e) Pleomorphic or linear calcifications. (f) The presence of architectural distortion.

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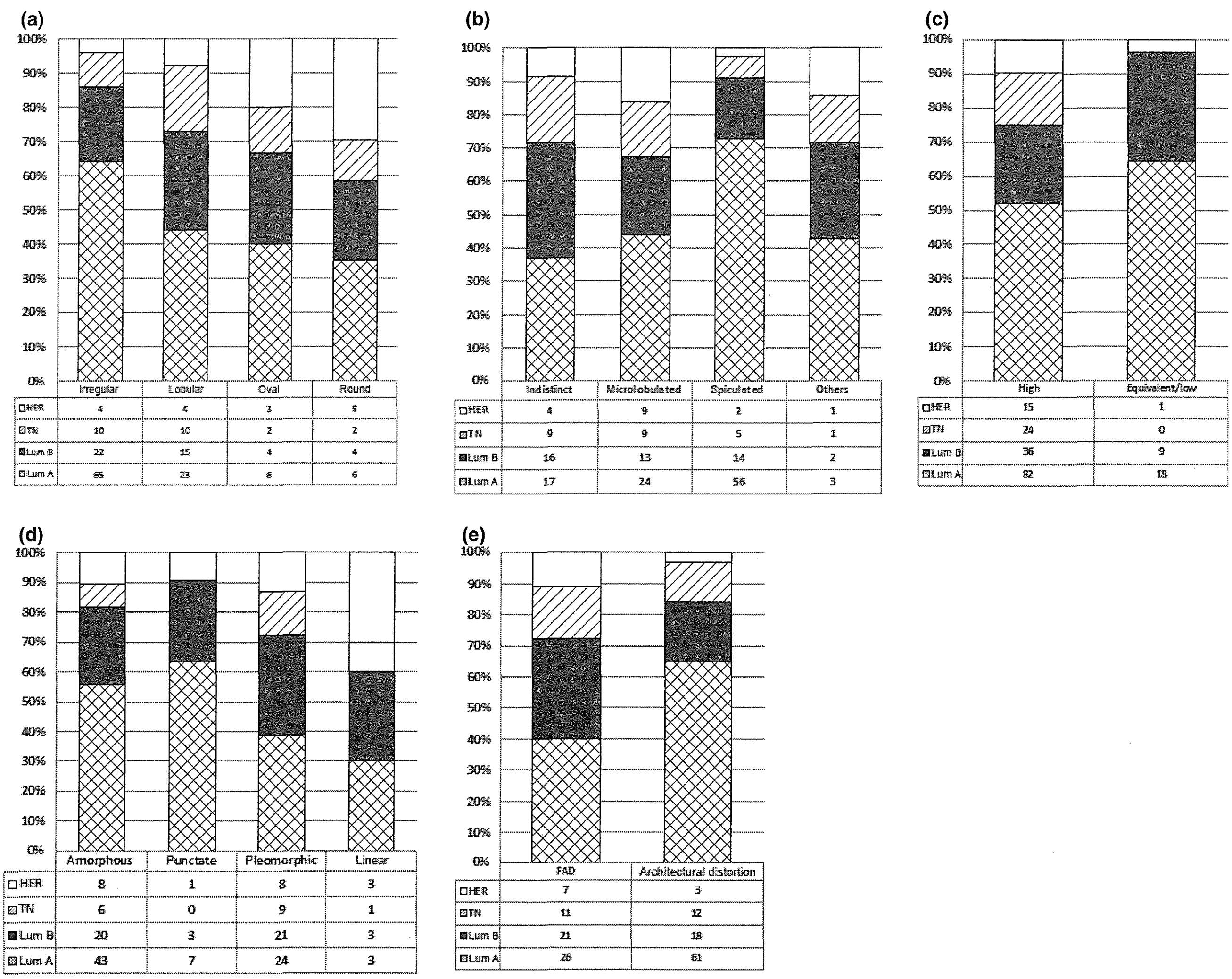
signal ratio (FISH score) >2.2.[14] Histological grades were assessed according to the criteria of Elston and Ellis.[4] The Ki-67 immunoreactivity was evaluated by examining high-power fields and counting 1000 tumor cells in the hot spots.[15] In addition, the presence or absence of lymphovascular invasion was determined according to *Rosen's Breast Pathology*.[12] Intrinsic subtypes were classified according to the St Gallen international expert consensus on the primary therapy of early breast cancer 2011[16] as follows: luminal A was ER and/or PgR positive, HER2 negative, and Ki-67 low (<14%); luminal B was either ER and/or PgR positive, HER2 negative and Ki-67 high, or ER and/or PgR positive, any Ki-67, and HER2 overexpressed or amplified; the HER type was HER2 overexpressed or amplified and ER and PgR absent; and triple negative was ER, PgR and HER2 negative.

We compared mammographic findings, including mass shape, margin, density, calcification, FAD, and architectural distortion, with the histopathological characteristics of the tumors, including intrinsic subtype, histological grade, lymphovascular invasion, and the Ki-67 labeling index.

Statistical analysis. To compare mammographic findings with histopathological findings, multivariate analysis was used. All analyses were performed using SPSS version 10.0 (SPSS Inc., Chicago, IL, USA), with $P < 0.05$ taken to indicate significant differences.

Results

Comparison of mammographic findings with intrinsic subtype. Figure 2 summarizes the results of the numbers and ratios of each mammographic finding according to intrinsic subtype. In the luminal A group, significant differences were identified between masses that were irregular and lobular or round ($P = 0.017$ and $P = 0.024$), between those that had speculated and indistinct or microlobulated margins ($P < 0.001$ and $P = 0.001$), between those showing amorphous and pleomorphic calcification ($P = 0.044$), and between the presence and absence of architectural distortion ($P = 0.002$). In the HER group, significant differences were identified between masses that were irregular and oval or round ($P = 0.009$ and $P < 0.001$), between masses that were lobular and round ($P = 0.021$), and between those that had spiculated and microlobulated margins ($P = 0.005$). In the triple negative group, significant differences were identified between masses that had spiculated and



(a)

	Irregular	Lobular	Oval	Round
HER	4	4	3	5
TN	10	10	2	2
Lum B	22	15	4	4
Lum A	65	23	6	6

(b)

	Indistinct	Microlobulated	Spiculated	Others
HER	4	9	2	1
TN	9	9	5	1
Lum B	16	13	14	2
Lum A	17	24	56	3

(c)

	High	Equivalent/low
HER	15	1
TN	24	0
Lum B	36	9
Lum A	82	18

(d)

	Amorphous	Punctate	Pleomorphic	Linear
HER	8	1	8	3
TN	6	0	9	1
Lum B	20	3	21	3
Lum A	43	7	24	3

(e)

	FAD	Architectural distortion
HER	7	3
TN	11	12
Lum B	21	18
Lum A	26	61

Fig. 2. Correlation between mammographic findings and intrinsic subtype: (a) mass shape, (b) margin, (c) density, (d) calcification shape, and (e) focal asymmetric density (FAD) and architectural distortion. HER, human epidermal growth factor receptor; TN, triple negative; Lum A, luminal A; Lum B, luminal B.

indistinct margins ($P = 0.027$), as well as between those identified as having high and equivalent or low density ($P = 0.027$).

Comparison of mammographic findings with histological grade. Figure 3 summarizes the results of the numbers and ratios of each mammographic finding according to histological grade. There were significant differences between irregular and lobular or oval mass shape in Grade 3 ($P < 0.001$ for all). Furthermore, in Grade 1 tumors, significant differences were found between with an indistinct and microlobulated or spiculated periphery ($P = 0.030$ and $P = 0.003$), between those with spiculated and indistinct or microlobulated margins ($P < 0.001$, respectively), between those identified as high and equivalent or low density ($P = 0.047$), and between those with a linear and amorphous calcification shape ($P = 0.027$).

Comparison of mammographic findings with lymphovascular invasion. Figure 4 summarizes the results for the numbers and ratios of each mammographic finding according to lymphovascular invasion. There were significant differences between oval and irregular or round mass shape ($P = 0.008$ and $P = 0.034$), between microlobulated and indistinct periphery ($P = 0.014$), between punctate and amorphous or pleomorphic calcification shape ($P = 0.030$ and 0.038), and between presence and absence of architectural distortion ($P = 0.027$).

Comparison of mammographic findings with the Ki-67 labeling index. Figure 5 summarizes the results of correlations between mammographic findings and the Ki-67 labeling index. The Ki-67 labeling index according to mass shape was 15.74 ± 6.21 for irregular masses, 38.82 ± 13.10 for lobular masses, 36.22 ± 15.75 for oval masses, and 37.85 ± 14.95 for round masses. According to mass periphery, the Ki-67 labeling index was 35.80 ± 28.51, 34.56 ± 29.76, 11.73 ± 10.86, and 27.50 ± 24.75 for tumors with indistinct, microlobulated, spiculated, and ''other'' margins, respectively. For tumors with a high and equivalent or low mass density, Ki-67 labeling index was 27.68 ± 26.75 and 13.14 ± 14.10, respectively. Tumors that showed amorphous, punctate, pleomorphic, and linear calcification had a Ki-67 labeling index of 24.55 ± 7.58, 26.00 ± 18.27, 24.68 ± 9.43, and 16.00 ± 17.23, respectively. In tumors without and with architectural distortion, the Ki-67 labeling index was 22.27 ± 8.64 and 25.02 ± 7.43, respectively. There were significant differences between irregular and lobular or round ($P < 0.001$ and $P = 0.014$), spiculated and indistinct or microlobulated ($P < 0.001$ for all), and high and equivalent or low density ($P = 0.018$) groups. A trend for a positive correlation was detected between irregular and oval mass shape, but the difference did not reach statistical significance ($P = 0.062$).

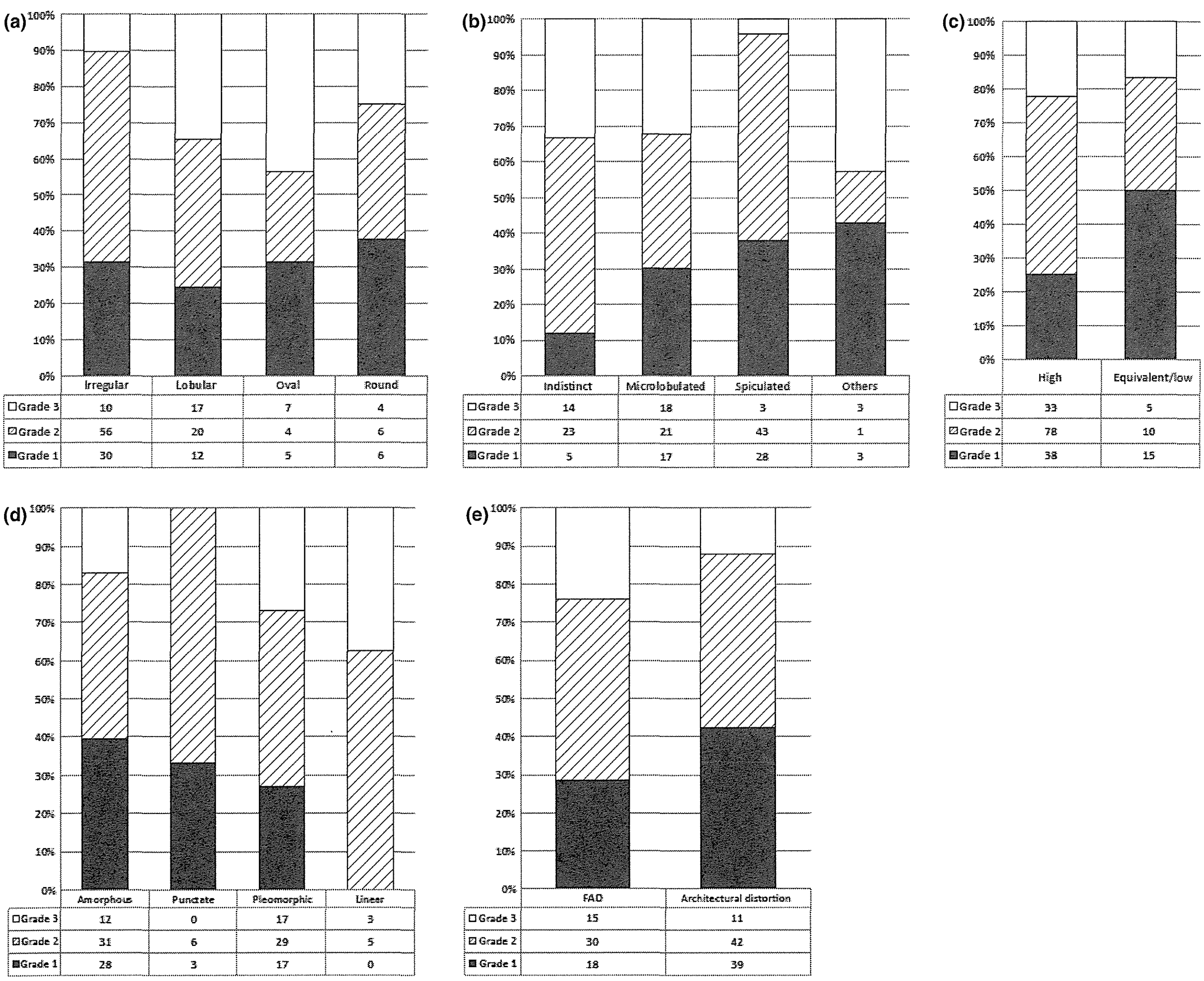


Fig. 3. Correlation between mammographic findings and histological grade: (a) mass shape, (b) margin, (c) density, (d) calcification shape, and (e) focal asymmetric density (FAD) and architectural distortion.

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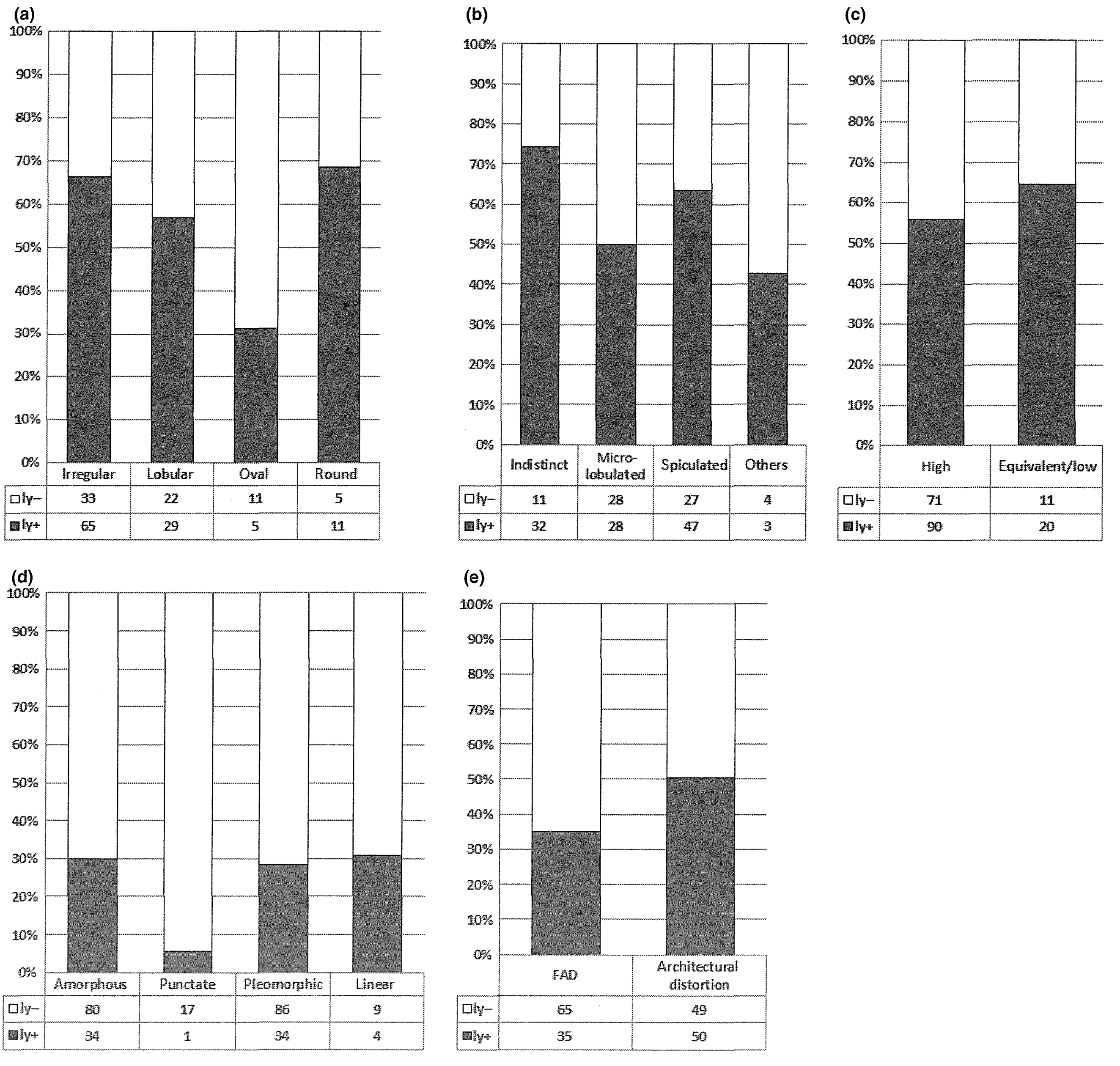

Fig. 4. Correlation between mammographic findings and lymphovascular invasion: (a) mass shape, (b) margin, (c) density, (d) calcification shape, and (e) focal asymmetric density (FAD) and architectural distortion. ly–, no lymphovascular invasion; ly+, lymphovascular invasion.

There were no significant differences according to calcification shape and the presence of architectural distortion.

Discussion

Histological grade is well known to have a strong correlation with clinical outcome in patients with breast cancer.[4] Accumulating clinical evidence suggests that prognostic factors influencing breast cancer extend beyond the traditional tumor histological grade.[17] Several factors, including ER expression, HER2 status, and lymphovascular invasion, have been clearly demonstrated in recent years to contribute significantly to the management and subsequent prognosis of patients with breast cancer.[7,18] Therefore, an accurate correlation between mammographic findings and their corresponding histopathological features is considered most important in mammographic evaluation. Mammographic findings may provide insights into pathological and biological features, including tumor cell characteristics, histological grade, and cell proliferation. We attempted to determine which finding is more relevant with regard to the newly defined subtype of breast carcinoma cells. Therefore, the purpose of the present study was to evaluate the correlation between mammographic findings (e.g. mass shape, margin, density, calcification shape, FAD, and the presence of architectural distortion) with intrinsic subtype, histological grade, lymphovascular invasion, and the Ki-67 labeling index in breast cancer patients.

Several previous studies evaluated the correlation between mammographic findings and histopathological characteristics in individual patients.[8,19–21] A number of independent groups demonstrated that masses with a spiculated periphery were associated with a good outcome in patients.[19,20] Conversely,

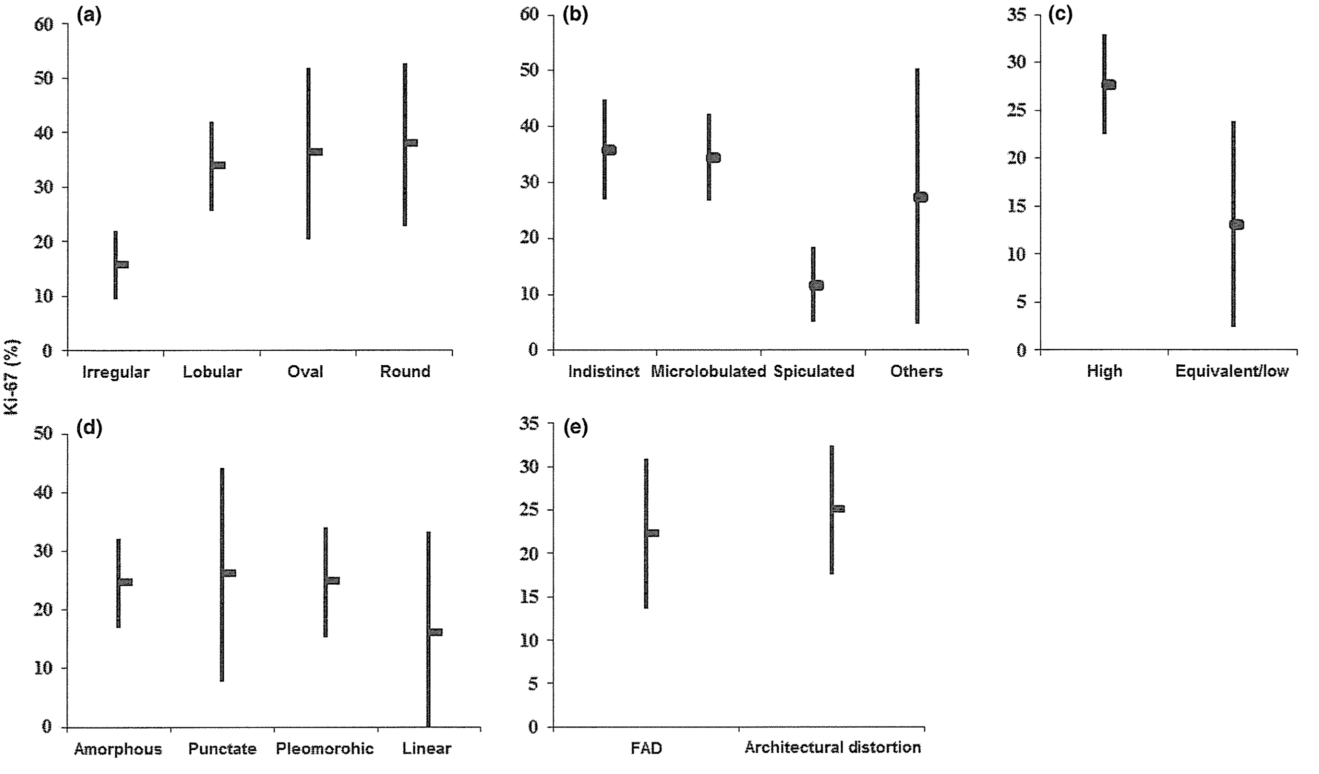

Fig. 5. Correlation between mammographic findings and Ki-67 labeling index: (a) mass shape, (b) margin, (c) density, (d) calcification shape, and (e) focal asymmetric density (FAD) and architectural distortion.

well-defined masses were associated with triple-negative breast cancer.[8,21] The results of the present study demonstrate that is a higher incidence of lower histological grade in masses with an irregular shape and/or spiculated margins, although a higher histological grade is not necessarily associated with irregular mass shape or spiculated margins. In addition, correlation of mammographic findings with the intrinsic subtype demonstrated that irregular mass shape and/or spiculated margin masses were significantly more frequently detected in luminal A breast cancers than in the other subtypes in this cohort of Japanese patients. However, oval and round mass shape and/or indistinct and microlobulated margin masses were significantly more frequently detected in triple-negative breast cancers or HER breast cancers. As for architectural distortion, the ratio of architectural distortion was significantly higher in luminal A cases and also tended to be associated with histological Grade 1. Together, these results suggest that poorly differentiated breast carcinoma cells are associated with good histological grade and luminal A subclassification. However, well-differentiated carcinoma cells are associated with adverse clinical grading and negative ER status.

Previous studies have demonstrated that these differentiations were related somewhat with adhesion factors.[22,23] Loss of adhesion factors in carcinoma cell is considered to play a role in the characteristic histological appearance of invasive carcinoma as loosely dispersed linear columns of cells and a typical discrete mass.[22] This more diffuse infiltrative pattern may explain some of the typical imaging appearances of tumors, such as spiculation and distortion.[22] In addition, adhesion factors are correlated with high histologic grade.[23] Therefore, adhesion factors may be considered to be correlated with the results of the present study in that spiculated breast cancers have a good clinical outcome and histological Grade 1. However, it is also true that numerous biological mechanisms underlying the association between the process of infiltration and histopathological characteristics remain unknown and that further investigations are required to confirm interpretation of mammography in terms of the biological and histopathologic characteristics of tumors.

To the best of our knowledge, this is the first study to compare mammographic findings with the Ki-67 labeling index and histopathological lymphovascular invasion. The results of the present study demonstrated that there was a higher incidence of a lower Ki-67 labeling index in tumors with an irregular mass shape, spiculated periphery, and equivalent or low mass density. Irregular mass shape and a spiculated periphery are well-known predictors of malignancy, but the results of the present study seem to suggest that findings of irregular shape and a spiculated periphery are relatively good prognostic predictors in terms of the Ki-67 labeling index. In addition, the results of the present study demonstrate that lymphovascular invasion was significantly greater in cases in which there was architectural distortion; however, the incidence of lymphovascular invasion was not significantly higher in spiculated masses. These results all suggest that the correlation between findings of radiological dist ortion and the mechanisms of lymphovascular invasion remain unknown and further investigations are required.

We also examined the correlation between mammographic calcification shape and histopathological characteristics. Previous studies have reported that triple-negative breast cancers are more likely to exhibit comedo calcifications.[8] In addition, the high frequency of comedo calcification in triple-negative breast cancers may represent a consequence of high histologic grade.[8] The presence of mammographic comedo calcification has also been reported to be associated with a poor prognosis in small screening-detected invasive cancers.[19] The results of the present study also demonstrate that non-necrotic calcifications, including amorphous and punctate calcification, are associated with a higher ratio of luminal A cases, whereas necrotic calcifications, including pleomorphic and linear calcification, were

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associated with a higher ratio of HER breast cancers. In addition, necrotic calcifications tended to be associated with a higher histological grade than non-necrotic calcifications. Therefore, the results suggest that the type of calcification may become a prognostic factor for breast malignancies.

We noted significant differences in the mammographic features of different primary breast cancer immunophenotypes in the present study. Stratifying the mammographic features according to immunophenotypes reveals distinct differences among cancer subtypes. However, the limitations of the present study include that fact that the study was retrospective in nature and was performed in a single institute, namely Tohoku University Hospital. Therefore, further investigations are needed, including analysis in several different institutions to further refine the new mammographic criteria. Biological and histopathological differences may result in imaging differences that may help us better understand the development of breast cancer. These proposed mammographic diagnostic criteria based on biological characteristics may contribute to a more accurate prediction of the biological behavior of breast malignancies.

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Disclosure Statement

The authors have no conflict of interest.

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Intracytoplasmic Lipid Accumulation in Apocrine Carcinoma of the Breast Evaluated With Adipophilin Immunoreactivity: A Possible Link Between Apocrine Carcinoma and Lipid-rich Carcinoma

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Abstract: Although apocrine carcinoma is a distinct histologic entity, there is no immunohistochemical marker to confirm apocrine differentiation with high sensitivity and specificity, and its differential cytologic characteristics are still not fully clarified. Despite the foamy cytoplasm of some apocrine carcinomas and the existence of lipid in the normal apocrine gland, intracytoplasmic lipid in apocrine carcinomas has not been fully explored. By using immunohistochemistry for adipophilin, which is a specific marker of lipid accumulation that can be applied to paraffin sections, we examined intracytoplasmic lipid in apocrine carcinomas. Twenty-four of 26 (92%) apocrine carcinomas and 38 of 116 (33%) nonapocrine carcinomas contained intracytoplasmic lipid. The frequency of adipophilin-positive cases was significantly higher in apocrine carcinomas compared with nonapocrine carcinomas ($P < 0.01$). The positive cell rate per tumor ranged from 10% to 70% (mean, 29%) for apocrine carcinomas. The staining density was heterogeneous from cell to cell. There was no difference in the staining pattern of adipophilin between apocrine ductal carcinoma in situ and invasive apocrine carcinoma or between eosinophilic cells and foamy cells. Sporadic or mosaic distribution of adipophilin-positive cells throughout the tumor and microvesicular or fine granular cytoplasmic staining with heterogeneous density were characteristic features of apocrine carcinoma. Although intracytoplasmic lipid was identified in most apocrine carcinomas, none of the apocrine carcinomas contained prominent intracytoplasmic lipid in >90% of the tumor cells; thus, the criteria for lipid-rich carcinoma was not fulfilled. However, the immunohistochemical study suggests that lipid-rich carcinomas are closely related to apocrine carcinomas.

Key Words: apocrine carcinoma, intracytoplasmic lipid, lipid-rich carcinoma, adipophilin, paraffin sections

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Apocrine carcinoma of the breast is defined as a carcinoma showing cytologic and immunohistochemical features of apocrine cells in >90% of the tumor cells.[22] The cytologic features of apocrine differentiation are abundant eosinophilic granular or foamy cytoplasm and a large nucleus with prominent nucleolus. Apocrine carcinomas are immunohistochemically characterized as estrogen receptor negative, progesterone receptor negative, bcl-2 negative, androgen receptor (AR) positive, and gross cystic disease fluid protein 15 (GCDFP-15) positive.[2,5,9,10,12,19,20] The diagnosis of typical apocrine carcinoma is usually straightforward; however, the histologic recognition of sebocrine and histiocytoid variants of apocrine carcinoma is occasionally subjective. There is no commercially available and stable immunohistochemical marker that is both sensitive and specific to apocrine differentiation. The reported frequency of apocrine carcinoma is variable depending on the definition of apocrine carcinoma that is used. On the basis of the findings of hematoxylin and eosin (HE)-stained sections, the frequency is 0.3% to 4%.[16] On the basis of the GCDFP-15 staining pattern, the frequency is 12% to 72%.[5,16] This variability reflects the discrepancy between apocrine carcinoma defined by histologic criteria and apocrine carcinoma defined by the apocrine markers that are present. Thus, unique cytologic features of apocrine carcinoma that differentiate it from other breast carcinomas with similar cytologic features are still not fully characterized.

The histology of the normal apocrine gland is characterized by luminal cells composed of eosinophilic cytoplasm, which may contain lipid, iron, lipofuscin, glycogen granules, and a large nucleus located near the base of the cell.[13] We focused on the relationships between intracytoplasmic lipid in the normal apocrine gland and in the foamy cytoplasm of some apocrine carcinomas. Although the foamy cytoplasm reminds us of the presence

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