ORIGINAL ARTICLE

Efficacy of Mammographic Evaluation of Breast Cancer in Women Less Than 40 Years of Age: Experience from a Single Medical Center in Taiwan

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Background/Purpose: Mammography is the standard imaging modality for breast cancer diagnosis. However, the value of mammographic diagnosis in breast cancer patients aged less than 40 years old has not been well assessed. The goal of our study was to determine the diagnostic efficacy of mammography for the detection of breast cancer in women under 40 years of age in a single medical center in Taiwan.
Methods: Of 1766 women diagnosed with breast cancer in one medical center between 1999 and 2005, 227 (12.9%) who were younger than 40 years of age were enrolled, and 105 of these 227 patients had pre-biopsy mammograms available for analysis. The sensitivities for mammography at first (prospective) and second (retrospective) readings and for corresponding ultrasound were calculated. The distribution of different breast composition between the mammographic true-positive (TP) and false-negative (FN) lesions at the first and second readings was analyzed.
Results: Of the 105 patients, 104 presented with a palpable mass and the other one was asymptomatic. There were 109 pathologically proven breast cancers from the 105 patients; 92 of 109 cancerous lesions were detected at the first mammographic reading (sensitivity 84.4%), and the most common mammographic sign was microcalcifications (40.2%). The second reading detected seven additional cancers (99 of 109 lesions; sensitivity 90.8%). There was no significant difference between mammographic TP and FN lesions for the different breast composition on first and second readings. Ninety patients also had ultrasound available for correlation with 94 cancers diagnosed from them. The diagnostic sensitivity of ultrasound was 94.7% (89 of 94 lesions).
Conclusion: Mammography has an acceptable sensitivity for the detection of breast cancer in women aged less than 40 years, regardless of different breast composition. Breast ultrasound can offer a higher sensitivity for such a population. [*J Formos Med Assoc* 2007;106(9):736–747]

Key Words: breast neoplasms, diagnosis, mammography

Mammography is the standard imaging modality for breast cancer screening and regular mammographic surveillance is recommended for high-risk women and the general population over 40 years of age.[1,2] However, mammography would not appear to be an effective screening test for women younger than 40 years of age for four relevant reasons. First, the relative sensitivity of mammography for detecting breast cancer can be somewhat reduced for dense breasts, which

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often occur among younger women.[3–5] Second, mammographic surveillance with clinical breast examination among younger women would appear to feature a relatively low accuracy for detecting breast cancers, especially in carriers of a *BRCA* gene mutation. The possible reasons for such an outcome include a greater rate of growth of tumors among such women, the presence of atypical findings seen on mammograms and specific histopathologic characteristics in carriers of *BRCA* mutations.[6] Third, the breast tissue in younger women tends to feature increased radiation sensitivity, which encourages attending clinicians and radiologists against the use of mammography. Fourth, the incidence of breast cancer among younger women is relatively lower than in their older counterparts.[4] Nowadays, mammography would appear to be often used for symptomatic women younger than 40 years old. However, some published papers documented the low diagnostic yield of mammography for young women with symptoms, especially if they presented with a palpable mass.[7,8] On the other hand, a number of other studies have reported that mammography is a promising diagnostic tool for young women suffering from breast cancers.[4,5] However, the aforementioned series focused on the studies of younger-aged women in Western countries. On the other hand, the breasts of Asian women are usually smaller and denser than those of their Western counterparts.[9] In our country, it was reported that false-negative (FN) cancers on mammograms occurred more often in denser breasts (heterogeneous or extremely dense breasts), compared to true-positive (TP) cancers on mammograms.[9] However, the research was on women of all age groups with breast cancer, not only on younger-aged women (< 40 years). Actually, there is a higher percentage of younger-aged women with dense breast parenchymal pattern compared with their older counterparts.[5] Herein, we present the mammographic findings for a large series of women with breast cancer at our institute, all of whom were aged less than 40 years at the time of diagnosis. Further, we also attempted to estimate the relative diagnostic accuracy of mammography for breast cancer, and the overall role of mammography in the diagnosis of younger-aged women afflicted by breast cancer in Taiwan.

Materials and Methods

Patient collection

From a retrospective review of the chart records of our hospital, a total of 1766 women were diagnosed with breast cancer between April 1999 and June 2005 and underwent definitive surgery in our institution. Of these, 227 women (12.9%) were diagnosed before 40 years of age. Of the 227 women, 44 underwent mammograms after excisional biopsy for the cancer but before definitive surgery, 36 patients received only breast ultrasound examinations before surgery, and 42 patients were referred from outside institutes so their preoperative mammograms were not available, thus leaving 105 patients who had their pre-biopsy mammograms performed in our hospital and which were available for analysis. Of the 105 patients, 90 received corresponding pre-biopsy breast ultrasound in our hospital with the results available for correlation; all of these ultrasonographic examinations were performed by experienced, fixed sonographic technicians under the supervision of breast surgeons or radiologists using HDI® 3000 or 5000 Ultrasound Systems (ATL Ultrasound, Bothell, WA, USA), and the clinical information of the patients were all available during the examinations.

The retrieval of the patients' medical records was approved by the institutional review board of our hospital. The patient lists during the study period were obtained from the Department of Cancer Registry, Office of Medical Records of our hospital.

Mammographic interpretation, analysis and correlation with breast ultrasound and histopathology

We used a dedicated mammographic unit (GE, Senographe DMR, Buc, Cedex, France) with 18 × 24 cm Min-R M or Min-R 2000 screen/film systems

(Eastman Kodak, Rochester, NY, USA) for the participants. The processing time was 90 seconds for each exposure. All mammograms were performed by fixed and qualified radiologic technicians in our department, and additional imaging workup such as spot compression views or spot magnification views with skin BB marker labeling were routinely performed for patients with clinically suspicious, palpable findings. The pre-biopsy mammograms of the 105 patients were read prospectively by on-site mammographers (first reading, with clinical information available for interpretation based on the questionnaires filled out by the patients) and retrospectively by a radiologist who had extensive experience in mammography (second reading, with all diagnostic mammographic views and final diagnoses available for interpretation). The breast composition for each patient, as revealed by mammograms, was estimated according to the ACR (American College of Radiology) lexicon, that is, ACR 1 represents "the breast is almost entirely fat", ACR 2 corresponds to "there are scattered fibroglandular tissues", ACR 3 represents "the breast is heterogeneously dense", and ACR 4 is "the breast is extremely dense". Tumor size, predominant mammographic manifestations of breast cancers present and their corresponding breast ultrasonographic findings prior to biopsy were analyzed and compared with the corresponding histopathologic findings for study participants. The histology types and grades of the cancers were also recorded. The second reading of the pre-biopsy mammograms was also compared with the first reading prior to biopsy. Further, the distribution of different breast compositions between TP and FN lesions at the first and second mammographic readings were also categorized and estimated.

The mammographic assessment was categorized as: TP, if the cancers could be recognized on imaging as BI-RADS® (Breast Imaging Reporting and Data System) category 0 (mammographic assessment is incomplete, need additional imaging evaluation), BI-RADS® category 4 (suspicious finding, biopsy is recommended), or BI-RADS® category 5 (highly suggestive of malignancy), according to ACR BI-RADS® either on the first or second reading. A FN result was defined as: a cancer that could not be identified and was interpreted as normal (BI-RADS® category 1) or benign (BI-RADS® category 2) or probably benign (BI-RADS® category 3) on imaging, either on the first or second reading.

Statistical analysis

The mean size of mammographic TP lesions at the first and second readings were compared with corresponding histopathologic results using paired Student's *t* test. The mean pathologic size of the mammographic TP and FN lesions at the first and second readings was compared using Wilcoxon rank sum test. The distribution of breast composition between mammographic TP and FN lesions at the first and second readings was tested using Fisher's exact test. A p value < 0.05 was considered to be statistically significant.

Results

During the period of patient enrolment, a total of 109 pathologically proven breast-cancerous lesions from 105 patients were diagnosed. The ages of the 105 patients ranged from 26 to 39 years (mean, 34.93 ± 3.48 years; median, 35 years). Seven (6.7%) of them had their breast cancers diagnosed before 30 years of age. Only one of the 105 patients was asymptomatic, and this patient had a cancer revealing clustered microcalcifications on mammography, which was nonpalpable. The reason why she presented for mammography was to receive a routine follow-up after an excisional biopsy for a benign fibroadenoma in a different quadrant of the breast. The other 104 patients featured clinically relevant palpable masses, with the duration of patient-experienced symptoms ranging from 7 days to 10 years (mean, 8.44 months; median, 2 months), with all the palpable lumps corresponding to the cancerous lesions. Twenty-one of the 105 patients (20%) experienced symptoms for a period longer than 12 months, and 14 of 105 (13.3%) suffered from symptoms lasting longer than 24 months—they presented to a medical clinic due to recent enlargement of their pre-existing masses. Of the 105 patients, 24 (22.8%) were nulliparous and one (1.0%) was pregnant at the time of their cancer diagnosis. Nine of 105 patients (8.6%) revealed a family history of breast cancer. Twenty-four of 105 patients (22.8%) had given birth to their first baby before 30 years of age, and only one of these 24 patients (4.2%) had a family history of breast cancer.

Of the 109 pathologically proven cancerous lesions, 92 lesions were detected on mammography by on-site radiologists (first reading), featuring a sensitivity of 84.4% and a FN rate of 15.6%. Further, seven additional cancers (a total of 99 cancerous lesions) were detected at the second mammographic reading, featuring a sensitivity of 90.8%, and a FN rate of 9.2%. Of the 17 FN lesions missed by the first mammographic reading, 13 of 17 cancers were unifocal solitary findings from different patients, with all of the 13 lesions recognized by ultrasound. Breast ultrasound detected a total of three additional multifocal cancers in two patients. One patient had a FN lesion lying in close proximity to the major TP cancer, the two lesions were considered to be in the same palpable area according to the chart record, and ultrasound detected both lesions. Another patient had three FN satellite lesions that were again located very close to a major TP cancer, and all four lesions corresponded to the same palpable region. The corresponding ultrasound of this patient detected two of the three satellite cancers compared to the first mammographic finding. The FN satellite lesions of the two aforementioned patients were again missed at the second mammographic reading.

Of the seven women who had had their breast cancers diagnosed before 30 years of age, one featured a solitary cancerous focus that could not be detected either at the first or second mammographic reading (one FN lesion, Figure 1).

The dominant mammographic findings for the 92 TP lesions detected at the first mammographic reading and those for the 99 TP lesions revealed at the second reading are summarized in Table 1. Of the 92 TP lesions detected at the first mammographic reading, 37 lesions (40.2%)

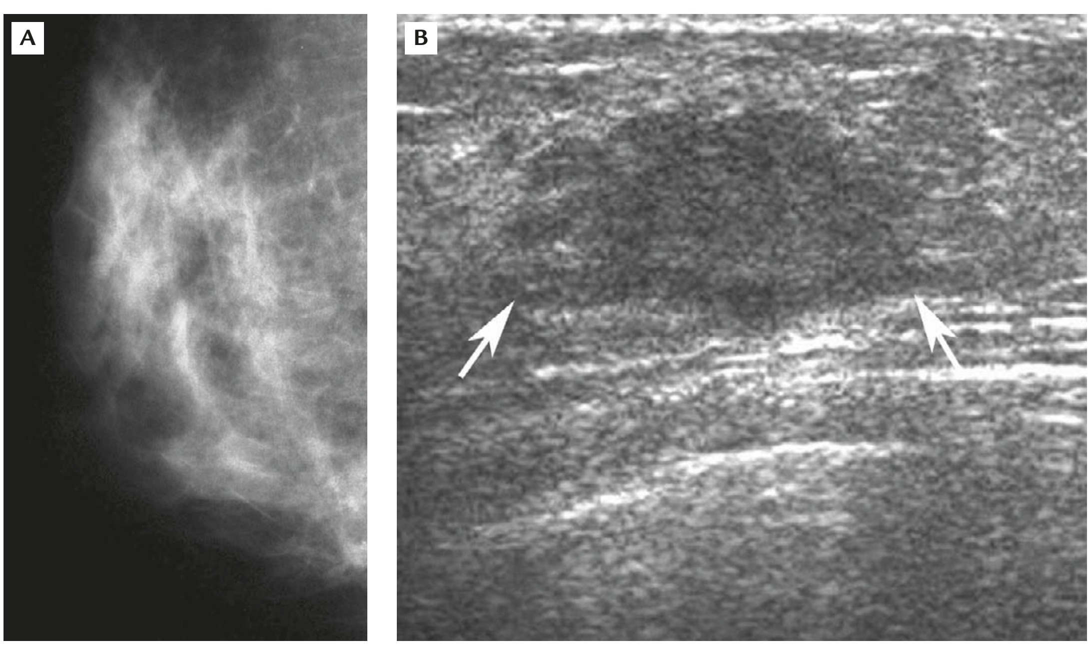

Figure 1. Right breast cancer in a 29-year-old woman who had a palpable lump in the right lower outer quadrant. (A) Right mammogram shows no definite mammographic abnormality even in retrospective review. (B) Directed breast ultrasound reveals an irregular, hypoechoic mass (arrows) with parallel orientation, measuring about 2.16 cm across the largest diameter, in the lower outer quadrant of the right breast. Histopathology revealed a grade III infiltrating ductal carcinoma.

Table 1. Dominant mammographic findings for the true-positive lesions at the first and second mammographic readings*

Finding	First reading†	Second reading‡
Microcalcifications	37 (40.2)	38 (38.4)
Focal asymmetry or architectural distortion	19 (20.6)	21 (21.2)
Mass	13 (14.1)	13 (13.2)
Focal asymmetry/architectural distortion + microcalcifications	11 (12.0)	12 (12.1)
Mass + microcalcifications	11 (12.0)	11 (11.1)
Skin/nipple retraction	1 (1.1)	3 (3.0)
Trabecular thickening	0 (0)	1 (1.0)
Total	92 (100)	99 (100)

Data are presented as n (%); †prospective reading; ‡retrospective reading.

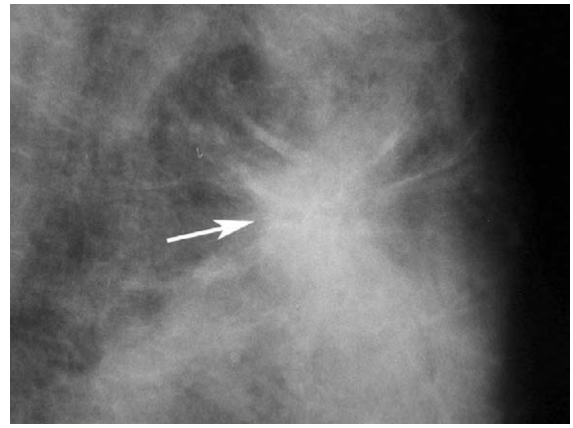

Figure 3. Left breast cancer in a 27-year-old woman. Left mammogram depicts a spiculated mass measuring 2 cm in size in the left breast (arrow). A grade II infiltrating ductal carcinoma was diagnosed on histopathology.

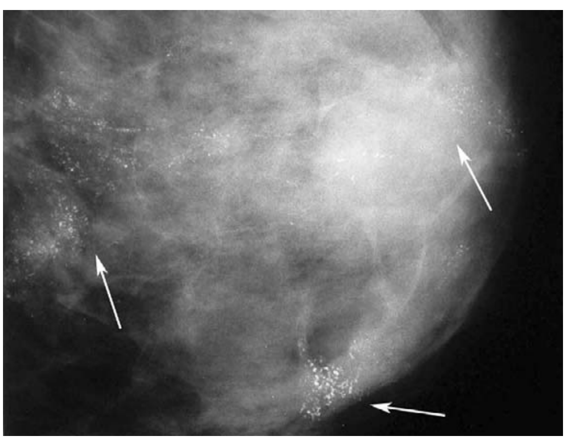

Figure 2. Left breast carcinoma in a 39-year-old woman who felt a huge palpable lump in the left breast. Baseline left mammogram shows extensive linear, branching and pleomorphic microcalcifications in the left breast (arrows). Histopathology revealed an infiltrating ductal carcinoma measuring 9 cm in size with axillary lymphadenopathies.

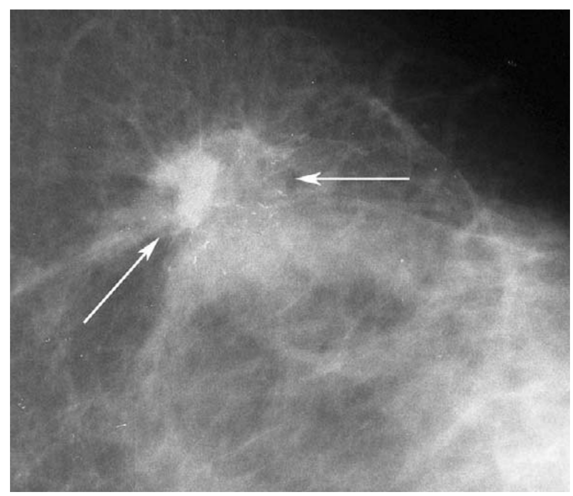

Figure 4. Left breast cancer in a 28-year-old woman who had felt a palpable lump in her left breast for 4 months. Left mammogram shows an irregular mass associated with pleomorphic and linear microcalcifications (arrows). The mass measured 2.5 cm across the largest diameter. Histopathology revealed a grade II infiltrating ductal carcinoma.

presented, predominantly, as microcalcifications (Figure 2), 19 lesions (20.6%) showed focal asymmetry or architectural distortion, 13 lesions (14.1%) were identified as a mass featuring a suspicious finding (Figure 3), 11 lesions (12.0%) had focal asymmetry or architectural distortion with microcalcifications, and 11 (12.0%) were identified as a mass with microcalcifications (Figure 4). There were 64.2% and 61.6% of TP cancers detected at the first and second mammographic readings, respectively, which presented as microcalcifications with or without associated signs (Table 1).

Of the seven breast cancers that were recognized only at the second mammographic reading and that were missed at the first reading, one featured clustered microcalcifications with a 1-cm dimension, two revealed focal asymmetry (Figure 5), one exhibited focal asymmetry with clustered microcalcifications, two demonstrated architectural

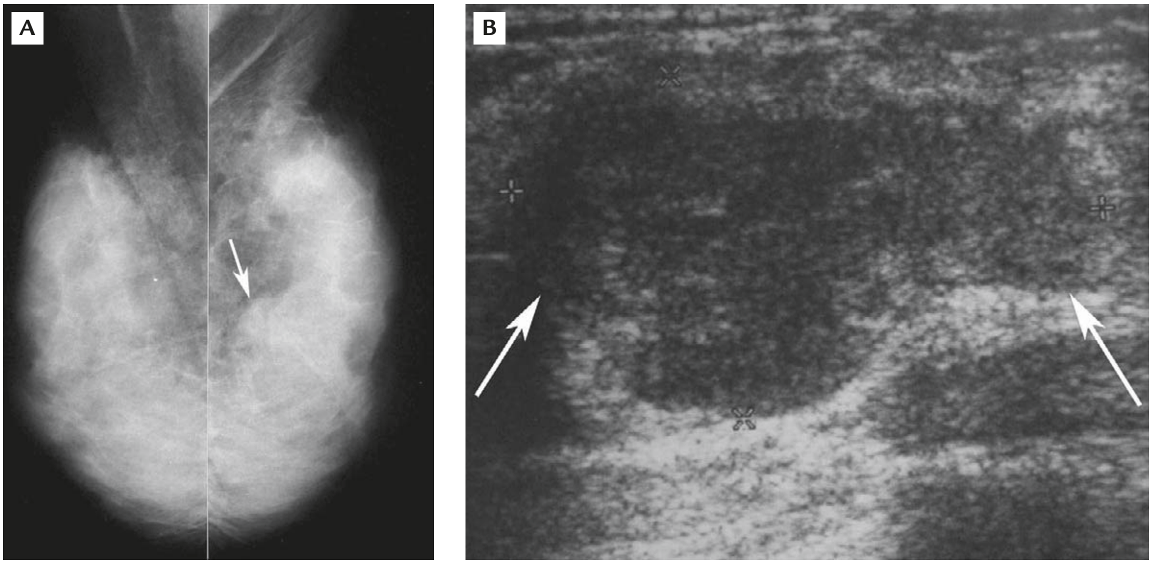

Figure 5. Left breast cancer in a 30-year-old woman who had a palpable lump in the 12 o'clock position of her left breast. (A) Bilateral mammograms (left breast on the right hand side, right breast on the left hand side) reveal a focal asymmetry (arrow) in the left breast, corresponding to the area of the palpable lump. However, the finding was recognized at the second mammographic reading but not identified at the first reading. (B) The corresponding breast ultrasound shows a microlobulated hypoechoic mass (arrows) in the 12 o'clock position of the left breast, measuring 1.5 cm across the largest diameter. Histopathology revealed a medullary carcinoma.

Table 2. Mean size of the mammographic true-positive lesions at the first and second mammographic readings with histopathologic correlation*

	Mammographic size,† cm	Pathologic size,‡ cm	p§
First reading ($n = 92$)	3.22 ± 2.19	3.07 ± 2.01	0.463
Second reading ($n = 99$)	3.14 ± 2.17	3.05 ± 1.99	0.654

**Data are presented as mean ± standard deviation; †mammographic size of lesions; ‡pathologic size of the mammographic true-positive lesions; §paired Student's t test.*

distortion with skin/nipple retraction, and the remaining one depicted subtle trabecular thickening (Table 1). Of the 37 lesions presenting as only microcalcifications at the first mammographic reading (Table 1), 31 had breast ultrasound available for correlation and 30 lesions presented as an evident irregular mass on ultrasound, leaving one FN lesion missed on ultrasound. The FN case on ultrasound presented as a cluster of mammographically visible microcalcifications spanning about 1 cm at pathology. The second mammographic reading detected one additional cancer showing faint clustered punctate microcalcifications measuring 1 cm on mammography but 2.5 cm at pathology, and the lesion was also depicted as a 2-cm mass on ultrasound.

The mean and median sizes of all the 109 pathologically proven lesions at histopathology were 2.93 ± 1.92 cm and 2.5 cm, respectively. The mean size of TP lesions at the first and second readings (measured from mammograms and histopathology), and TP and FN lesions at histopathology are summarized in Tables 2 and 3. On histopathology, the mean size of the mammographically determined TP lesions was larger than that of the FN lesions at the first and second readings, but the difference was only statistically significant for the second reading ($p = 0.004$) (Table 3).

Of the 105 study-participating patients, only four (3.8%) had minimally dense breast parenchyma (ACR 2), 68 patients (64.8%) had heterogeneously dense breasts (ACR 3), and 33 patients

Table 3. Mean pathologic size of mammographic true-positive (TP) and false-negative (FN) lesions at the first and second mammographic readings*

	TP		FN		$p^{\dagger}$
	n	Size, cm	*n*	Size, cm	
First reading	92	3.06 ± 2.01	17	2.18 ± 1.05	0.119
Second reading	99	3.03 ± 1.97	10	1.60 ± 0.54	0.004

**Data are presented as mean ± standard deviation; †Wilcoxon rank sum test.*

Table 4. Distribution of breast composition between mammographic true-positive (TP) and false-negative (FN) lesions at the first and second mammographic readings

	ACR 2,* *n* (%)	ACR 3,† *n* (%)	ACR 4,‡ *n* (%)	$p^{\S}$
First reading				0.455
TP	4 (4.3)	63 (68.5)	25 (27.2)	
FN	0	10 (58.8)	7 (41.2)	
Second reading				0.283
TP	4 (4.0)	68 (68.7)	27 (27.3)	
FN	0	5 (50.0)	5 (50.0)	

**ACR 2 is scattered fibroglandular tissue; †ACR 3 is heterogeneously dense breasts; ‡ACR 4 is extremely dense breasts; §Fisher's exact test.*

(31.4%) exhibited an extremely dense breast parenchymal pattern (ACR 4). We detected no significant difference with regard to breast composition distribution between TP and FN lesions at the first and second mammographic readings (Table 4).

A total of 90 among the 105 patients had both mammographic and sonographic examinations available for evaluation and a total of 94 cancerous lesions were diagnosed histopathologically. Of these 94 lesions, 89 were detected on ultrasound, such detection featuring a sensitivity of 94.7% and a FN rate of 5.3%. On the other hand, 77 of the 94 corresponding lesions were detected at the first mammographic reading, such detection featuring a mammography cancer-detection sensitivity for these patients of 81.9% and a FN rate of 18.1%. From the second mammographic reading of these patients, mammograms were able to detect 84 of 94 lesions (sensitivity, 89.4%). Among the other 15 patients without available breast ultrasonographic examinations for correlation, a total of 15 cancerous lesions were diagnosed at histopathology. The pathologic size of the 15 lesions did not differ significantly from those of the 94 cancerous lesions from 90 patients who had both mammograms and ultrasound available for correlation (Wilcoxon rank sum test, $p = 0.914$, two-tailed). Both the first and second mammographic readings detected the 15 lesions, and their dominant mammographic findings were: microcalcifications (7 lesions), focal asymmetry with microcalcifications (3), mass with microcalcifications (2), irregular mass (2), and architectural distortion (1).

Of the 109 pathologically proven cancers, 76 (69.7%) were classified as infiltrating ductal carcinoma (IDC), followed by ductal carcinoma *in situ* (DCIS) (12 lesions, 11.0%), IDC with DCIS (11 lesions, 10.1%), invasive lobular carcinoma (ILC) (4 lesions, 3.70%), medullary carcinoma (2 lesions, 1.83%), mucinous carcinoma (2 lesions, 1.83%), IDC and ILC (1 lesion, 0.92%), and intraductal papillary carcinoma (1 lesion, 0.92%). Of the 17 FN lesions at the first reading, 11 lesions were identified as IDC, followed by IDC with DCIS (2), ILC (2), medullary carcinoma (1), and intraductal papillary carcinoma (1).

Of the 10 FN lesions at the second reading, seven were IDC, followed by ILC (2), and medullary carcinoma (1).

Discussion

Breast cancer occurs rarely among young women.[10,11] Approximately 5.9–7% of breast carcinoma occurs before 40 years of age,[10,11] and approximately 2% of breast carcinoma occurs before the age of 35,[4,5] according to reported literature in Western countries. Breast cancer among younger-aged women has been reported to progress at a more rapid rate, and features a poorer prognosis compared with that for their older counterparts.[11–16] In Asia, the reported incidence of breast cancer in young Asian women (<40 years) was 12.6% in Singapore.[13] Han et al reported that 12.5% of breast cancers occurred under 35 years of age in Korea.[14] The other series in our country reported that 29.3% of breast cancer patients were diagnosed at the age of 40 or younger.[15] For our hospital, the incidence of breast cancers diagnosed for women under 40 years of age constituted 12.9% of the total number of breast cancer patients; the percentage is slightly higher than corresponding figures in Western countries, but relatively similar to the results from Asian countries.[4,5,10,11,13,14] The reasons for the higher incidence of early-onset breast cancer in Asian countries are not clear, and may be investigated from etiologic and epidemiologic factors.[15]

A family history of breast cancer tends to occur more frequently in women with early-onset breast cancers in some series, compared with breast cancers that develop later in life, with the former ranging from 24% to 37%, according to the reported literature in Western countries.[17,18] However, in Asian countries, only 8.7–13% of women with early-onset breast cancer had a family history of breast cancer.[15,16] For our study, 8.6% of our patients had a family history of breast cancer, with this figure appearing to be much lower than those reported in Western countries,[17,18] but relatively comparable to the reported series from Asian countries.[15,16] Women with germline mutations of *BRCA1* and/or *BRCA2* and mutations of other genes may feature another contributor to early-onset breast cancer.[16,19] Choi et al reported that the prevalence of *BRCA1* and *BRCA2* mutations in Korean women with breast cancer at a young age (≤40) was higher than that in Western countries.[16] Therefore, ethnicity may be another contributor to early-onset breast cancer, the influence of such a factor possibly explaining why a greater incidence of breast cancer occurs in younger-aged women in Asian countries compared to their Western counterparts. Nevertheless, we did not analyze the possible germline mutations in our study since no such detailed clinical data regarding this issue were available for our study population.

From our study, 24 of 105 (22.8%) patients were nulliparous and only one patient (1.0%) was pregnant at the time of cancer diagnosis. Nulliparity or an advanced maternal age at the time of the first birth has been reported to be a factor in the increased risk of developing breast cancer in later life.[10] However, a considerable proportion of patients (24 of 105) from our study delivered their first child before 30 years of age. It was also reported that the risk of premenopausal breast cancer is increased in women who have recently given birth.[12] From our study, however, there was only one example of pregnancy-associated breast cancer. Therefore, the relationship between factors of a recent birth or pregnancy and breast cancer cannot be readily assessed.

Women younger than 40 years of age are not routinely screened by mammography. Therefore, it is not surprising that almost all of the patients in our study had the chief complaints of palpable lumps. In our study, only one cancer from one patient was nonpalpable. There were another two patients with satellite FN cancers missed by mammograms but lying very close to the major TP cancers, with the FN lesions corresponding to the same palpable area as the TP findings. We even encountered delayed diagnoses of breast cancers for more than 2 years subsequent to the initial appearance of symptoms of palpable lumps. The delayed diagnosis was most likely due to non-belief, since breast carcinoma is rare in younger-aged women. For younger-aged women exhibiting related symptoms, it was reported that sonography is more accurate than mammography for cancer cancer diagnosis, since the sensitivity of mammography is reduced in younger, denser breasts.[8] Ultrasound and diagnostic fine-needle aspiration are recommended for symptomatic younger-aged women.[10] On the other hand, from our study, the relative sensitivity of diagnostic mammography for the detection of breast carcinoma in younger-aged women is quite acceptable regardless of breast composition (Table 4). However, since most of the study participants revealed dense breasts on mammograms (ACR 3 or 4), and none showed ACR 1 and only four had ACR 2, we can explain the results seen in Table 4 as that the sensitivity of mammography in our study was still acceptable even in dense breasts, when compared with other reported series.[3,9,20,21] Further, there were seven patients whose breast carcinomas were diagnosed before the age of 30, and there was only one FN result from mammography in this group. Clearly, the relative sensitivity of such determination was acceptable, and it was comparable to many other reported series.[3,9] However, it should be stressed that the sensitivity and FN rate as revealed by our study were estimated according to young patients, and the data appeared to differ from much of that reported previously in the literature. Previously reported overall FN rates for mammography have ranged from 8% to 30%,[3,9] most of which were based on results obtained from older asymptomatic screening populations. Mann et al reported in 1983 that the FN rate for symptomatic patients in their series was 34.2%.[20] However, the other paper has reported a much lower FN rate of 8.6% for symptomatic patients.[21] In fact, the above-mentioned studies focused on all age groups from Western countries,[3,20,21] not simply on younger-aged women. From the few available studies focusing on younger-aged women in Western countries, reported sensitivity ranged from 69.2% to 86%, with most of the involved individuals in these studies being symptomatic,[4,8] and such a scenario is similar to our study of an Asian population. The relatively acceptable results of mammography from our study could be explained by two factors. First, most of the mammographic TP cancers in our study revealed microcalcifications with or without other associated signs (Table 1) on mammograms, and the sign of microcalcifications can be well recognized even if the finding is in dense breasts. Second, almost all (104) of the 105 patients were symptomatic with only one exception, and the mean pathologic tumor size of TP cancers on mammograms was larger than 3 cm in diameter (Tables 2 and 3), thus causing the lesions to be more easily recognized on mammograms. Our study demonstrated that 20% and 13.3% of study-participating patients had experienced symptoms related to breast cancer for more than 1 and 2 years, respectively. We cannot presume that mammography could also have been used effectively to detect these cancers 1–2 years prior to their actual diagnosis, at which time the lesions would likely have been smaller than at the time of actual diagnosis. However, from our study and other literature,[4,5] for the younger-aged women with symptoms, mammography can provide important information in certain situations, such as when searching for a primary malignancy, aid in characterization of a suspicious palpable finding and indication of a biopsy, and further delineation of the extension of a lesion.

In our study, seven additional cancers were recognized at the second mammographic reading with variable mammographic findings (Table 1). According to the literature, the most common mammographic findings for FN lesions that failed to be recognized at the first reading but are depicted at retrospective readings are ill-defined mass, focal asymmetry, or architectural distortion.[3,9] Breast cancers showing microcalcifications were seldom missed by mammography.[3,9] In our study, however, there were two of seven FN lesions missed at the first reading but that were depicted at the second reading, revealing mammographically visible microcalcifications with or without associated sign (Table 1), although mammography is the most reliable imaging tool to delineate microcalcifications.[3] Knowledge of the possible mammographic findings of FN lesions can help us interpret mammograms more cautiously and thus reduce the FN rate. Some series reported the importance of independent double reading for mammography, which can cause an increase of up to 15% in the cancer detection rate.[22,23] However, the aforementioned series focused only on a screening population, instead of symptomatic women like in our study.

In addition, though there were 40.2% and 38.4% of lesions at the first and second mammographic readings, respectively, presenting only with the mammographic sign of microcalcifications (Table 1), most of these lesions can still be recognized on the corresponding ultrasound as a mass. The reason for why the sign of a mass was not depicted on mammograms was most likely due to the lesions being obscured by superimposed, dense breast tissue, resulting in only the sign of microcalcifications being detected on mammograms. The reason why the one lesion showing microcalcifications on mammograms was missed by ultrasound was most likely because of its relatively small size.

The actual tumor size at histopathology of the mammographic TP lesions at the first mammographic reading was somewhat larger than was the case for the FN lesions, although such difference did not prove to be significant (Table 3). However, such difference at the second mammographic reading proved to be statistically significant (Table 3). Such results appeared to be compatible with results presented in a number of studies to the effect that mammographic FN cancers tend to be smaller than corresponding TP lesions.[3,9]

In our study, 90 of 105 study-included patients had available pre-biopsy mammograms and ultrasound results that could be reviewed for comparison. Breast ultrasound would appear to have a higher sensitivity than first and second mammographic readings in these patients. This was not surprising because the relative sensitivity of mammography is somewhat reduced for young, dense breasts.[8,20] Further, it has been reported that ultrasound is a reliable adjunct for younger-aged, symptomatic patients when mammographic readings are negative, as mentioned above.[8] For symptomatic patients, negative mammographic results should not preclude the possibility of biopsy,[20] and ultrasound is strongly recommended for further evaluation.[8] Breast ultrasound is also a reliable adjunct to mammography in the preoperative evaluation of patients with breast cancers, especially in dense breasts and when breast conservation is planned.[24] Berg et al reported that breast ultrasound depicted 15% of multifocal or multicentric breast cancers in patients suspected of having unifocal disease by mammograms; in addition, there were 16 patients in their study who had multifocal or multicentric cancers diagnosed by mammograms, and ultrasound detected two additional foci in a patient.[24] In our study, ultrasound detected three additional multifocal cancers than mammograms in two patients.

On the other hand, from our study, there were 15 cancers from 15 patients without ultrasound available for correlation, and all of the 15 lesions were detected at the first and second mammographic readings. Though we cannot obtain the ultrasound records for the 15 patients, and the mammographic findings revealed variable appearances, the actual pathologic tumor size of the corresponding 15 cancers did not differ from those of other patients who had ultrasound available for comparison. Therefore, according to our result that most TP cancers with mammographically detected microcalcifications can be depicted on ultrasound, we might presume that ultrasound can still feature an acceptable detection rate for these 15 lesions, even if there were seven of 15 lesions manifesting as only microcalcifications on mammograms.

For the purposes of our study, we did not further investigate the pathology types of breast carcinoma suffered by these younger-aged women, since most of the patients in our study presented with a pathology type of IDC, a condition quite similar to their older counterparts.

Early detection of breast cancer may be an important issue for the sake of enhancing the life expectancy of women suffering from breast cancer at a relatively younger age. Though mammography is the standard modality for breast cancer screening, its relative sensitivity is somewhat poorer for younger dense breasts than for older, fatty breasts, as has been mentioned above.[5,20] It was reported that screening breast sonography could detect more occult breast cancers that are not detected on mammography or physical examination, and such a benefit is especially obvious among women with dense breasts and increased risk of breast cancer.[25–27] However, because most of the younger-aged patients in our study did not have a family history of breast cancer, and most of them were symptomatic at the time of presentation, we cannot presume that these young women without obvious risk of breast cancer would have benefited from ultrasound screening if they had undergone ultrasound screening long before their cancers had become symptomatic.

Breast magnetic resonance imaging (MRI) is another possible option for breast cancer screening for young women.[2,28] Breast MRI has a high sensitivity for the detection of invasive breast cancer,[2,6] but the published results regarding breast MRI detection for *in situ* disease vary widely, with the sensitivity for detecting DCIS ranging from 40% to 100%.[2] Most previous breast MRI screening programs enrolled only women who had a positive family history of breast cancer and/or certain breast cancer-related germline mutations.[6,28] However, most women participating in our series featured neither a family history of breast cancer nor any available germline-mutation results. It is thus problematic with regard to whether MRI is suitable for routine breast cancer screening for younger-aged women without a family history of breast cancer.

In conclusion, from our study in Taiwan, 12.9% of women with breast cancer had their cancer diagnosed before the age of 40 years. Mammography has an acceptable sensitivity rate for the detection of breast cancer among women younger than 40 years of age, most of whom show dense breasts on mammograms and present with symptoms of palpable lumps, and most of whom feature signs of mammographically visible microcalcifications, and which therefore define mammography's impressive diagnostic value even in dense breasts. Breast ultrasonography can offer a slightly higher sensitivity than mammography for the detection of breast cancer for such a population.

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