RESEARCH ARTICLE

Editorial Process: Submission:05/31/2018 Acceptance:11/15/2018

Features of Microcalcifications on Screening Mammography in Young Women

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Abstract

Background: There is no decrease in the number of breast cancer deaths if screening mammography is performed in women aged <40 years. However, NCCN guidelines recommend screening mammography in young women at risk of hereditary breast cancer. Therefore, more accurate screening mammography for young women is needed. **Objective:** To evaluate the features of screening mammographic findings, particularly microcalcifications, in women aged <50 years to increase the positive predictive value of screening mammography in young women. **Methods:** We retrospectively reviewed the data of consecutive women who underwent opportunistic and organized breast cancer screening at the Sakuragaoka Hospital (Shizuoka, Japan) between April 2013 and March 2015. We compared the mammographic findings and features of microcalcifications between women aged <40 and 40–49 years and those aged 50–74 years. **Results:** The study included 3645 women. Of these 3645 women, 415 (11.4%) were aged <40 years, 1219 (33.4%) were aged 40–49 years, and 2011 (55.2%) were aged 50–74 years. Women aged <50 years were more likely to be recalled for microcalcifications than those aged 50–74 years (<40 years, 4.8%; 40–49 years, 4.3%; 50–74 years, 3.3%). Young women were more likely to be recalled for small round and segmental microcalcifications [<40 years, odds ratio (OR): 1.799 (95% CI: 0.751–2.846); 40–49 years, OR: 1.394 (95% CI: 0.714–2.074)] and less likely to be recalled for small round and grouped microcalcifications [<40 years, OR: 0.603 (95% CI: 0.181–1.025); 40–49 years, OR: 0.961 (95% CI: 0.496–1.428)] compared with women aged 50–74 years. **Conclusions:** On screening mammography, women aged <50 years had a higher tendency to be recalled for microcalcifications, particularly small round and segmental microcalcifications. False-positive results may be reduced by reflecting the characteristics of microcalcification findings among young women without breast cancer in the future.

Keywords: Mammography- breast cancer- young women- microcalcifications- screening

Asian Pac J Cancer Prev, **19 (12)**, 3591-3596

Introduction

Breast cancer frequently causes death among young women (Matsuda et al., 2013). Unfortunately, the sensitivity and specificity of mammography has been found to be lower in young women than in old women (Armstrong et al., 2007; Nelson et al., 2009). Screening mammography has helped reduce breast cancer mortality in women aged >50 years (Nystrom et al., 2002; Schopper and de Wolf, 2009). Although breast cancer screening is currently recommended for women aged >40 years in Japan, some studies have found that false-positive results were much more common in women aged 40–49 years than in those aged 50–59 years (Mandelblatt et al., 2009; Nelson et al., 2009). Screening mammography is not recommended for young women aged <40 years because of low prevalence, radiation exposure, and dense breasts (Yankaskas et al., 2010; Myers et al., 2015). However, in Japan, screening mammography is often performed for young women aged <40 years at arbitrary screening and company checkups. Furthermore, NCCN guidelines recommend not only screening magnetic resonance imaging but also screening mammography for young women aged over 30 years at risk of hereditary breast cancer (Daly et al., 2017). With more widespread screening for hereditary breast cancer, accurate screening mammography for young women is expected.

To increase the specificity of screening mammography for young women and relieve the anxiety associated with a false-positive result, the reasons for the high rate of false-positive results in screening mammography among young women need to be identified. It is necessary to consider the factors associated with false-positive results in young women rather than the prevalence of breast cancer because the prevalence will be high on screening for hereditary breast cancer.

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Because of the high frequency of high-density breasts in young women, studies have assessed the characteristic findings in young women, particularly those with a mass and focal asymmetric density (Osako et al., 2007; Zhao et al., 2014). Few studies have examined the characteristics of breast microcalcifications on screening mammography in young women. A previous study showed that the positive predictive value of the current BI-RADS criteria markedly decreased in women aged <50 years and further decreased in those aged <40 years (Farshid et al., 2011). The types of mammographic findings and microcalcifications causing an increase in the false-positive rate among young women are unclear.

The Japanese guidelines for mammography and the BI-RADS categories are prepared based on the breast cancer risk estimated from the mammography findings of previous studies (Committee to Revise Mammography Guidelines, 2010; D'Orsi CJ, 2013). If the findings are often false positives, and if the relative risk of breast cancer is low in women aged <40 years, the classification of categories in young women should be reconsidered.

There is no study that reveals the characteristics of microcalcifications in young women without breast cancer. The purpose of this study was to examine the features of mammographic findings, particularly microcalcifications, in women aged <50 years. The study retrospectively compared the findings and microcalcifications on screening mammography between young and old women.

Materials and Methods

We retrospectively reviewed the data of consecutive women who underwent opportunistic and organized breast cancer screening the Sakuragaoka Hospital (Shizuoka, Japan) between April 2013 and March 2015. We excluded women with a history of breast cancer, those aged >74 years, and those not undergoing screening mammography.

Each screening mammogram is assessed by two certified radiologists for mammography by The Japan Central Organization on Quality Assurance of Breast Cancer Screening. They classify every mammogram into five categories based on the Japanese guidelines for mammography (Committee to Revise Mammography Guidelines, 2010). Our institute recalled the women who were diagnosed to be in category 3 or more on mammography for further examination at our hospital or other hospital. Depending on the results of the additional imaging studies, the clinician decide the diagnostic procedure and sent the results to our institute.

The primary endpoint of this study is the rate of microcalcification findings in young women aged <40 years and secondary endpoints are the rate of mammographic findings in each category. We classified the women according to age into those aged <40 years, those aged 40–49 years, and those aged 50–74 years. We compared the mammographic findings of women aged <40 years and those aged 40–49 years with the findings of women aged 50–74 years.

Our institute advised all women with recalled findings to receive precise examinations. Unfortunately, some women did not go to hospital and the doctors with whom other women consulted forgot to send our institute the results of the additional examinations. Therefore, the cases for which the results of the additional tests were reported to our institute were regarded as "Identified outcomes."

Mammographic findings used to recall women included microcalcifications, tumors, focal asymmetry density, and architectural distortion of the breast, and they were examined using the chi-square test. In addition, we reviewed mammographic microcalcifications with regard to distribution and morphology. Despite recall for microcalcifications, women with obvious benign microcalcifications on reevaluation were considered to have "benign" lesions. The distribution included benign, grouped, and segmental microcalcifications. The morphology included benign, small round, amorphous, and coarse heterogeneous types. Because both small round and amorphous microcalcifications are equivalent to secretory microcalcifications, amorphous calcifications are analyzed as small round microcalcifications (Committee to Revise Mammography Guidelines, 2010). We considered mineralized lesions that were pathologically breast cancer as "malignant calcifications" and other mineralized lesions as "benign calcifications."

Crude odds ratio (OR) and 95% confidence intervals (95% CIs) were estimated for the associations between the mammographic findings of women aged <40 years and 40–49 years and the findings of those aged 50–74 years. Particularly, we analyzed OR with "small round and segmental microcalcifications" and "small round and grouped microcalcifications" in women aged <40 years and 40–49 years. Data were analyzed using Stata/IC version 15.0 for Windows (StataCorp LLC, College Station, TX, USA). A P-value of <0.05 was considered significant.

Results

Study selection

Figure 1 shows the flow diagram for the study selection. The study included 3645 women. Of these 3645 women, 415 (11.4%) were aged <40 years, 1219 (33.4%) were aged 40–49 years, and 2011 (55.2%) were aged 50–74 years.

Age-specific modalities and results of breast cancer screening

There were no significant differences in the rate of additional screening ultrasonography between women aged <40 years and 40–49 years and those aged 50–74 years (Table 1). Two-view mammography (craniocaudal view and mediolateral oblique view) was performed significantly more frequently in women aged <40 years and 40–49 years than in women aged 50–74 years (<40 years, 9.9%; 40–49 years, 67.8%; 50–74 years, 3.1%; Table 1).

Table 1 also presents the results of breast cancer screening. Identified outcomes were less common in women aged <40 years and 40–49 years than in women aged 50–74 years (<40 years, 67.6%; 40–49 years, 67.0%; 50–74 years, 78.0%). Breast cancer was diagnosed in six women aged 50–74 years and two women aged

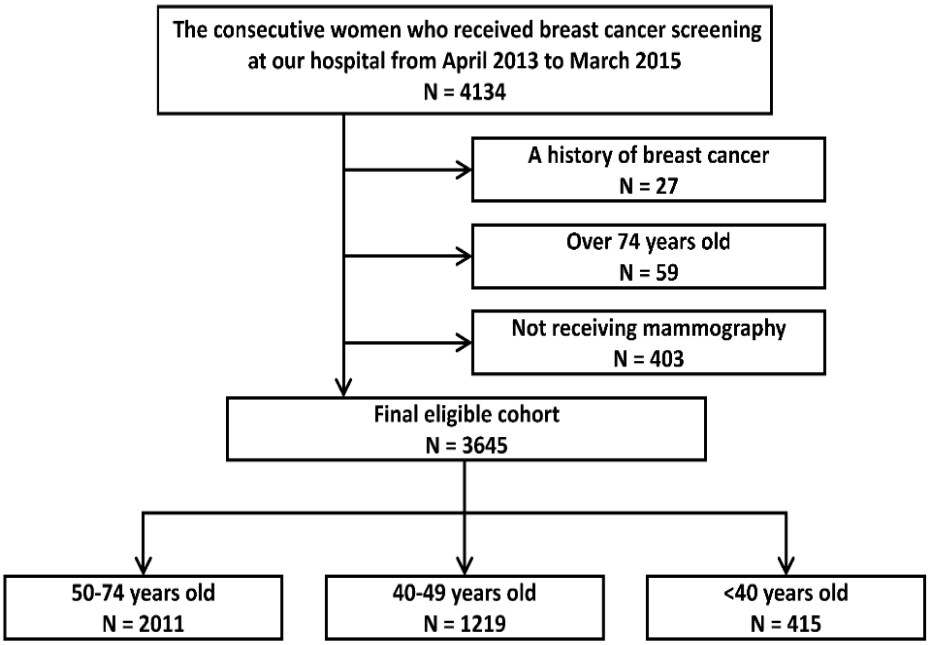

Figure 1. Inclusion Criteria and Age-Specific Classification

Table 1. Age-Specific Modalities and Results of Screening

	50–74 years old	40–49 years old		<40 years old	
	N = 2011	N = 1219	P-value	N = 415	P-value
Only MMG, n (%)	1,917 (95.3)	1,158 (95.0)	0.671	400 (96.4)	0.343
MMG + US, n (%)	94 (4.7)	61 (5.0)	0.671	15 (3.6)	0.343
Two-view, n (%)	62 (3.1)	827 (67.8)	<0.001	42 (9.9)	<0.001
Recall cases, n (%)	159 (7.9)	103 (8.4)	0.584	34 (8.2)	0.844
Identified outcome	124 (78.0)	69 (67.0)	0.048	23 (67.6)	0.199
cases, n (%)	124/159	69/103		23/34	
Breast cancer, n (%)	6 (0.30)	2 (0.16)	0.718	0 (0)	0.598
PPV	3.77	1.94	0.485	0	0.593

MMG, mammography; US, breast ultrasonography; Two-view, two-view mammography; PPV, positive predictive value

40–49 years. Breast cancer was not noted in women aged <40 years.

Mammographic findings

Figure 2 indicates typical mammograms with findings of (A)(B)"small round and grouped" and (C)(D)"small round and segmental" microcalcifications. Figure 2 (A)(C) indicates benign microcalcifications present in the young women included in this study. Contrarily, Figure 2 (B) (D) indicates malignant microcalcifications present in this eligible cohort.

There were no significant differences in mammographic findings of women aged <40 years and 40–49 years compared with those of women aged 50–74 years (chi-square test with 2×4 Table; 40–49 years: P = 0.125 and <40 years: P = 0.229). Women aged <40 years and 40–49 years were more likely to be recalled for microcalcifications (<40 years, 4.8%; 40–49 years, 4.3%; 50–74 years, 3.3%) and less likely to be recalled for other findings compared with women aged 50–74 years (Figure 3). However, the differences were not significant.

Univariate analyses for findings of microcalcifications

There tended to be more women who were scrutinized for microcalcifications among women aged <40 years and 40–49 years than among those aged 50–74 years (<40 years, OR: 1.469 [95% CI: 0.881–2.057]; 40–49 years, OR: 1.319 [95% CI: 0.913–1.725]; Figure 3). The most frequent combinations of distribution and morphology were "small round and segmental microcalcifications" and "small round and grouped microcalcifications" (42 [30%] and 41 [29%], respectively). The young women were more likely to be recalled for small round and segmental microcalcifications (<40 years, OR: 1.799 [95% CI: 0.751–2.846]; 40–49 years, OR: 1.394 [95% CI: 0.714–2.074]) and less likely to be recalled for small round and grouped microcalcifications (<40 years, OR: 0.603 [95% CI: 0.181–1.025]; 40–49 years, OR: 0.961 [95% CI: 0.496–1.428]).

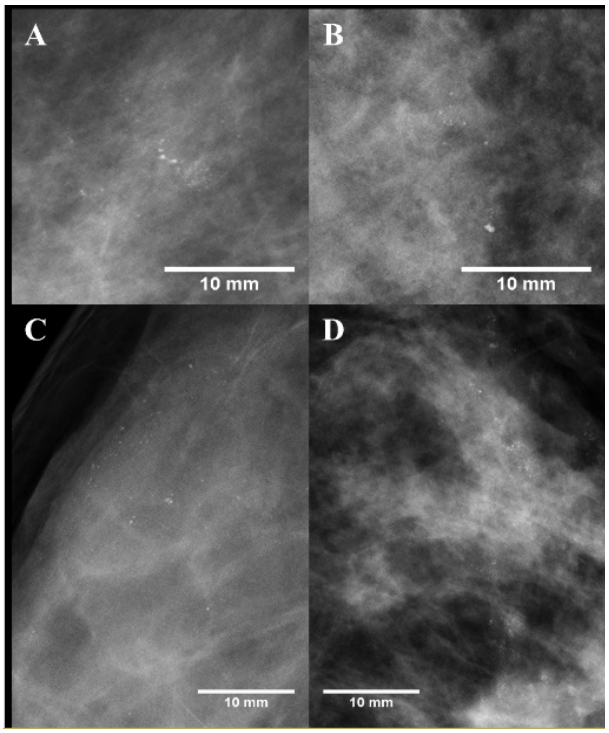

Figure 2. Screening Mammograms Showing (A)(B) "Small Round and Grouped" and (C)(D) "Small Round and Segmental" Microcalcifications. (A) Benign small round and grouped microcalcifications in a recalled woman (46 years old). (B) Malignant small round and grouped microcalcifications of the right breast in a recalled woman (47 years old). She underwent breast-conserving surgery and axillary lymph node resection. The final stage was T1c N2 M0 Stage IIIA. (C) Benign small round and segmental microcalcifications in a recalled woman (31 years old). (D) Malignant small round and segmental microcalcifications of the left breast in a recalled woman (55 years old). She underwent breast-conserving surgery and sentinel lymph node biopsy. The final stage was T1c N0 M0 Stage I.

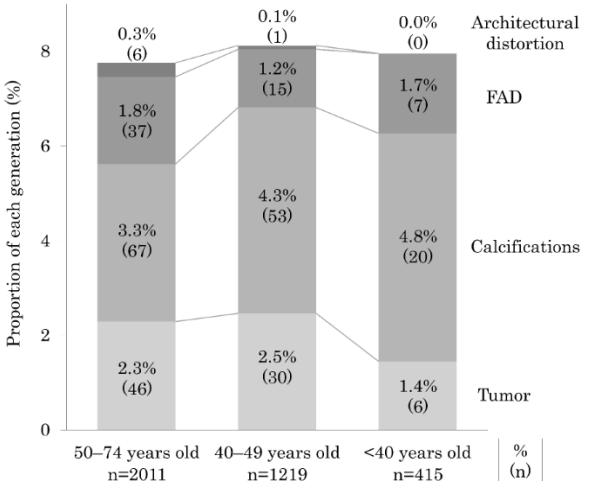

Figure 3. Each Mammographic Finding in Women Aged 50–74 Years, 40–49 Years, and <40 Years. There were no significant differences in mammographic findings of women aged <40 years and 40–49 years compared with that of women aged 50–74 years (chi-square test with 2 × 4 table; 40–49 years: P = 0.125 and <40 years: P = 0.229)

Discussion

To our knowledge, this is the first study to evaluate the features of mammographic findings in young Japanese women who were recalled based on screening mammographic findings. The study found that young women were more likely to be recalled for small round and segmental microcalcifications and less likely to be recalled for small round and grouped microcalcifications on screening mammography. This finding may be used to reduce the rate of false-positive results and increase specificity on screening mammography in young women by reconsidering mammographic categories among generations.

On breast cancer screening for young women, we should be aware of the features of mammograms in young patients with breast cancer to maintain high sensitivity. Zhao et al., (2014) showed that the number of young patients with a mammographic focus who had microcalcifications was significantly more than that of old patients (44.2% vs. 39.4%, P = 0.001). Additionally, considering the high prevalence of dense breasts among young women, microcalcifications are important findings in young patients with breast cancer. In all three patients who had breast cancer with microcalcifications in our study, no tumor was detected on mammography and microcalcifications were the only findings on mammography (Figure 2B, D).

Microcalcifications, which are important findings in young patients with breast cancer, have been previously evaluated. Farshid et al., (2011) analyzed the features of cases from the period 1992–2007 in which biopsy was performed and microcalcifications were the only imaging abnormalities. Among 2545 lesions, they reported that the rate of malignancy was significantly lower in women aged <50 years than in those aged 50–69 years (<50 years, 41.7% vs. 50–69 years, 48.1%) (Farshid et al., 2011). This result indicates that benign microcalcifications that raise confusion with regard to malignancy are more common in women aged <50 years, and this supports our results. The question now arises as to how accurate breast cancer

Table 2. Univariate Analyses for Findings of Microcalcifications

	50–74 years old N = 2011			40–49 years old N = 1219			<40 years old N = 415		
	n	OR	95% CI	n	OR	95% CI	n	OR	95% CI
Microcalcifications	67	1 [reference]		53	1.319	0.913–1.725	20	1.469	0.881–2.057
Small round and grouped	24	1 [reference]		14	0.961	0.496–1.428	3	0.603	0.181–1.025
Small round and segmental	29	1 [reference]		16	1.394	0.714–2.074	7	1.799	0.751–2.846

OR, odds ratio; CI, confidence interval

screening is based on microcalcifications in young women, despite intergenerational differences in the prevalence of benign microcalcifications.

It is difficult to explain the relationship between age and benign microcalcifications because there is no clarity on how calcifications are produced in breast cancer as well as in benign lesions (Cox and Morgan, 2013). A previous study has shown that in patients with dense breast tissue, an underlying proliferative histology with calcifications was observed significantly more frequently than that with noncalcified lesions (66.7% vs. 35.9%, RR = 2.3, p = 0.003) (Lewis et al., 2016). This finding suggests that having dense breasts may increase the occurrence of benign microcalcifications and that young women with dense breasts may have more frequent benign microcalcifications. In this study, there was no significant difference in the observations between benign microcalcifications and malignant microcalcifications in young women (Figure 2). Generally, it is difficult to distinguish between benign and malignant microcalcifications in young women because of the low rate of malignancy on breast biopsy in young women (Farshid et al., 2011).

We suggest that microcalcifications should be assessed using a modality other than mammography for screening in young women or that the categories for microcalcifications should be modified to reflect the different generations according to the high prevalence of benign microcalcifications in young women. The young women in our study were more likely to have "small round and segmental microcalcifications," which are generally classified in a worse category than "small round and grouped microcalcifications." This intergenerational discordance of distribution with regard to benign microcalcifications should be reflected in the screening category, and this may help reduce the false-positive rate of screening mammography.

The present study has some limitations. First, we could not identify all outcomes of additional examinations. The identified outcome rate was significantly lower in women aged 40–49 years than in women aged 50–74 years. The reason for this may be a higher examination rate for breast cancer in women aged <50 years in Japan (MHLW, 2011; Uchida et al., 2015). Second, we did not consider the screening interval and the availability of previous mammograms that have been mentioned to be associated with false-positive results (Hubbard et al., 2011). Unfortunately, we did not have interval information and did not know whether evaluators for breast cancer screening showed comparative readings to those of previous mammograms, as our institution was undergoing a transition to digital mammography. However, this could not explain our result that young women were more likely to be recalled for small round and segmental microcalcifications. Finally, considering that the cancer detection rate for women aged <40 years was low in opportunistic screening(Yankaskas et al., 2010), the sample size of this single-institution study was too small to analyze the cancer detection rate of each mammographic finding. Because several women receive screening mammography at 2-year intervals, duplications would increase if the research period was 2 years or more.

In conclusion, women aged <50 years, particularly <40 years, had a higher tendency to be recalled for microcalcifications than those aged 50–74 years on screening mammography. Particularly, <40 years tended to show higher rates of small round and segmental microcalcifications. It is suggested that false-positive results may be reduced by reflecting the characteristics of intergenerational microcalcification findings in the category classifications of screening mammography. Thus, future studies are required to determine the biological mechanisms of microcalcification formation associated with benign breast lesions and breast cancer cells.

Funding statement

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Statement conflict of Interest

None of the authors have any conflict of interest to declare.

Acknowledgments

We thank all the staff of the Sakuragaoka Hospital and the Department of Breast and Endocrine Surgery, The Jikei University School of Medicine, for their extraordinary support in this study process.

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