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Usefulness of Ultrasonography Combined with Conventional Physical Examination in Mass Screening for Breast Cancer: A Retrospective Study of Yamanashi Health Care Center Results from 1989 to 1994

Hirotaka Okamoto,[1,3] Tadahiko Ogawara,[1] Fumio Arihara,[1] Kazuhisa Kobayashi,[1] Shingo Inoue,[2] Kaoru Nagahori,[2] Masayuki Yamamoto,[2] Takayoshi Sekikawa[2] and Yoshiro Matsumoto[2]

[1]*Department of Health Care Center, Yamanashi Prefectural Welfare Federation of Agricultural Co-operatives, 3-2-44 Iida, Kofu, Yamanashi 400 and* [2]*First Department of Surgery, Yamanashi Medical University, 1110 Shimokato, Tamaho, Nakakoma, Yamanashi 409-38*

We retrospectively analyzed the records for 34,474 women who participated in mass screening for breast cancer by physical examination with or without ultrasonography (US) at Yamanashi Health Care Center between April, 1989 and March, 1994 to evaluate the usefulness of US in mass screening. In one group (15,935 women) conventional physical examination with inspection and palpation alone had been performed, and in another (18,539 women) both conventional physical and US examinations were performed. Breast cancer was detected in 27 of the women (0.08% of the total group screened), 22 of whom were in the group examined by US; moreover, 16 of these 22 women had early breast cancer, which was a non-palpable tumor in 13. Half of the 22 women were examinees under the age of 50 years. Of the 22 tumors detected in the groups examined by US, 16 (73%) were early breast cancer. The overall detection of early breast cancer (0.09%) in the US group was significantly higher than that (0.01%) in the group examined by conventional methods ($P < 0.05$). Of the tumors detected in the US group, 59.1% were non-palpable. These results suggest that early and non-palpable breast cancer can be detected using US, and the incidence of detection of such tumors in women under the age 50 years is increased in mass screening including US examination. This examination is effective in mass screening for breast cancer, especially for early and non-palpable breast cancer tumors.

Key words: Breast cancer — Mass screening — Ultrasonography — Detection rate — Non-palpable breast cancer

The incidence of breast cancer and its mortality in Japan have been increasing and this cancer is projected to become the second leading cancer in women by the year 2000.[1] Therefore, the importance of mass screening for early detection of this cancer is clear. Mass screening for breast cancer by physical examination is now a well-established practice in Japan. On the other hand, mammographic screening (MMG) is used for breast cancer screening in western countries and affords a reduction in breast cancer mortality in women aged 50 and over[2–5] and increased potential for breast-conserving treatment due to earlier detection.[6,7] In Japan, randomized studies of mammographic or ultrasonographic screening have not yet been carried out. The use of MMG for screening is recommended because screening limited to physical examination alone has been shown to afford only a low detection rate and to have no impact on mortality,[8,9] while screening with MMG was reported to improve the detection rate for breast cancer, especially early cancer in women aged 50 and over.[10,11] However, it was also reported that ultrasonography (US) is more useful than MMG for the detection of breast masses.[12–17]

In order to evaluate the usefulness of US in mass screening, we therefore retrospectively analyzed the records of a US mass screening program for breast cancer at our institute and at mobile screening stations at geographically distant areas compiled during a recent five-year period. Furthermore, we investigated, according to the staging of the breast cancers detected, approaches to the detection of early breast cancer in relation to the results of the initial or periodic screening and of clinical stage of the non-palpable breast cancer tumors.

SUBJECTS AND METHODS

Subjects We retrospectively reviewed the records of a total of 34,474 women who participated in our mass screening program for breast cancer during the five-year period between April, 1989 and March, 1994. Of them, 15,938 were examined at our institute (group Z) and 18,536 in mobile stations (buses).

Screening methods The screening conducted for all participants at our institute and for some participants at

[3] To whom requests for reprints should be addressed at the First Department of Surgery, Yamanashi Medical University.

the mobile stations (group Y) consisted of both physical examination with inspection and palpation and US examination. The screening program in group Y was begun in 1991. The remaining participants were examined at the mobile stations and received the physical examination alone, unless abnormal findings were found, in which event, US was also performed (group X). The physical examinations were performed by a physician. The US examination was conducted by technicians on bilateral dimensions of the breasts, horizontally and vertically, using a 10 MHz mechanical sector type probe (Aloka SSD650CL or 1200). The US scans were all recorded on videotape and images of any abnormal lesions were acquired on instant films for later inspection by the physician.

Classification of ultrasonographic findings The ultrasonographic findings for the women were divided into five grades, as follows: A, no abnormal finding; B, benign lesion, such as cyst, confirmed by follow-up for one year; C, benign lesion, followed up for 6 months, but in which malignancy could not be ruled out, such as hypoechoic mass with regular margin, echogenic spot, mammary ductectasia, heterogenous mammary gland; D, suspected malignant lesion, such as hypoechoic mass with irregular margin or echogenic spot, for which the participant was encouraged to undergo further examinations; and E, malignant lesion requiring immediate treatment.

Initial and periodic screening In every year the participants included both examinees being examined for the first-time and repeats (Fig. 1). The program in group Y was not begun until 1991, and for that reason all the examinees in that year were first-time examinees.

Definition of non-palpable and early breast cancer In this study, we defined non-palpable breast cancer as cancer that did not form a mass appearing as microcalcification on mammography, and that could be detected only by US at the time of mass screening. Early breast cancer was defined as a tumor with diameter of less than 2 cm as estimated by palpation, without detection of either metastatic lymph node or systemic metastasis.[18] Staging for breast cancer was done according to the General Rules of the Japanese Breast Cancer Society.[18]

Statistical analysis Statistical analysis of qualitative parameters was carried out using the chi-square test with comparisons among subgroups within groups or between groups.

RESULTS

Numbers of examinees and breast cancers detected in the five years As shown in Table I, the numbers of examinees both at the institute and through the mobile screening program generally increased year by year. The proportion of cases that required further examinations

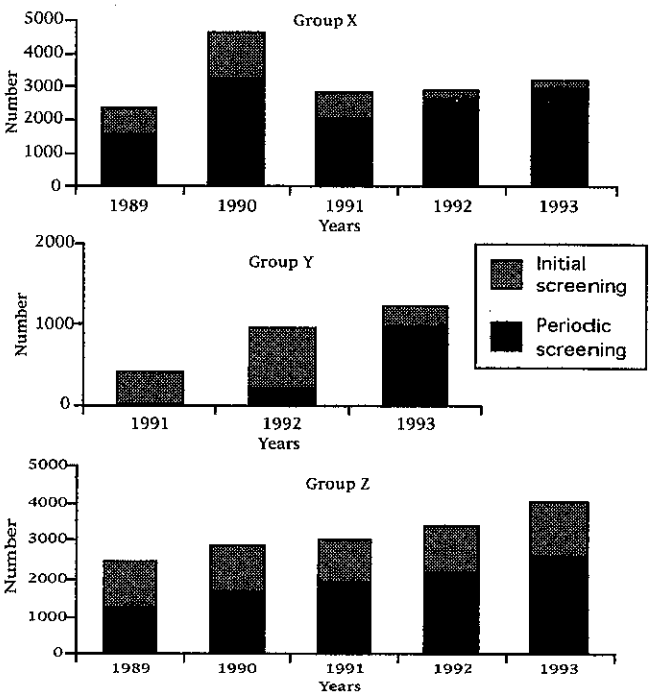

Fig. 1. Annual proportion of initial and periodic examinees. In every year the participants included both examinees being examined for the first-time and repeats. Group X, mobile station, physical examination; Group Y, mobile station, physical and US examination; Group Z, institute, physical and US examination.

ranged from 1.5% to 3.1% (mean rate: 2.4%). The number of patients with breast cancer found in the five years was 27, and the detection rate in each year ranged from 0.02% to 0.16% (mean rate: 0.08%). The age of the 27 participants in whom breast cancer was detected ranged from 32 to 76 years (mean age: 52.9 years).

Breast cancer detection in each group Table II shows for each group the overall number of examinees, mean age, number of participants with detection of breast cancer, and incidence of detection of breast cancer. The incidence was highest in group Y (0.23%), whereas the incidences in groups Z and X were 0.10% and 0.03%, respectively.

In group X, the incidence of detection was slightly higher among the repeat examinees (0.03%) than among the initial ones (0.02%), while in groups Y and Z, the opposite pattern was seen; the incidence was higher among the initial examinees (0.29% and 0.14%) than among the repeat ones (0.17% and 0.07%, respectively) (Table III). In no group was there a significant difference in incidence between the initial and repeat examinees. In groups Y and Z, examined by US, the incidence was higher than that in group X, examined initially by the

Table I. Annual and Total Numbers of Examinees in the Mass Screening for Breast Cancer: 1989–1993

Year	Total No. of examinees	No. of examinees at institute[a)]	No. of examinees in mobile screening[b)]	Rate of further examinations (%)	No. of examinees identified with cancer	Incidence of cancer detection (%)
1989	4,831 (2,035)	2,460 (1,224)	2,371 (811)	2.4	1	0.02
1990	7,608 (2,686)	2,923 (1,292)	4,685 (1,394)	1.5	2	0.03
1991	6,301 (2,323)	3,072 (1,161)	3,229 (1,162)	2.1	10	0.16
1992	7,276 (2,252)	3,449 (1,310)	3,827 (942)	3.1	6	0.08
1993	8,458 (1,934)	4,034 (1,433)	4,424 (501)	2.9	8	0.10
Total	34,474 (11,230)	15,938 (6,420)	18,536 (4,810)	2.4	27	0.08

Numbers in parentheses indicate the number of first-time examinees.
a) Yamanashi Health Care Center.
b) Mass screening for breast cancer at the area in which examinees live. Doctors and the practitioners travel there in a fully equipped bus.

Table II. Overall Incidence of Breast Cancer Detection in Each Mass Screening Group

Group	No. of examinees	Mean age ±SD (years)	No. of examinees with cancer	Incidence of cancer detection (%)	Mean age±SD of examinees with cancer (years)
X	15,935	55.4±14.0	5	0.03	61.0±15.1
Y	2,601	53.3±11.6	6	0.23	52.8±9.9
Z	15,938	51.9±9.3	16	0.10	49.3±7.6

Incidence of cancer detection: No. of participants with cancer detected/Total No. of examinees.

Table III. Number of Breast Cancers Detected at Initial and Periodic Screenings

Group	Initial screening (%)	Periodic screening (%)
X	1/3,409 (0.02)	4/12,454 (0.03)
Y	4/1,401 (0.29)	2/1,200 (0.17)
Z	9/6,420 (0.14)	7/9,522 (0.07)

Table IV. Clinical Stages of the 27 Patients with Breast Cancer Detected at the Screenings

Group	Stage							
	Initial screening				Periodic screening			
	I	II	III	IV	I	II	III	IV
X	0	1	0	0	2 (1)	2	0	0
Y	0	4	0	0	2 (1)	0	0	0
Z	7 (3)	1	1	0	7 (3)	0	0	0

Numbers in parentheses indicate the numbers of tumors 1.0 cm or less in diameter.

physical examination alone, but the difference was not significant.

Clinical stage of the 27 breast cancers detected at the mass screening The clinical stage of each of the 27 breast cancers detected in the mass screening is shown in Table IV. Seven of the 14 tumors detected at the initial screening were advanced (6 in stage II and one in stage III), whereas only 2 of the 13 tumors detected at the repeat screening were stage II tumors and all the others were stage I. Moreover, all 9 tumors detected in groups Y and Z at repeat screening were stage I, and 7 of the 9 detected at initial screening in group Z were stage I. Seven stage I tumors less than 1.0 cm in diameter were detected by US in groups Y and Z. Of the 22 tumors detected in groups Y and Z, 16 (73%) were early breast cancer. Only two (40%) of the 5 tumors initially detected by physical examination in group X were early tumors. The overall incidence of early breast cancer detection was 0.09% (16/18,539) in the two groups examined by US and 0.01% (2/15,935) in the group examined by physical examination alone.

Numbers of palpable and non-palpable tumors by clinical stage Thirteen of the 27 tumors were non-palpable, including 12 in stage I (Table V). Five of these 12 were

Table V. Numbers of Palpable and Non-palpable Tumors by Clinical Stage

Clinical stage (No. of tumors)		No. of examinees with palpable breast cancer	No. of examinees with non-palpable breast cancer
Stage I	T≦1.0 cm (8)	3	5
	T>1.0 cm (10)	3	7
Stage II	(8)	7	1
Stage III	(1)	1	0
Stage IV	(0)	0	0

Table VI. Age Distribution of All Examinees and the 22 Patients with Breast Cancer Detected by Physical and US Examination in the Screening

Age range (years)	Physical and US examination		
	No. of examinees (%)	No. of examinees with breast cancers (No. of early cases)	Incidence of cancer detection (%)
–29	178 (0.9)	0	0
30–39	1,473 (7.9)	2 (1)	0.14
40–49	5,747 (31.0)	9 (7)	0.16
50–59	6,026 (32.5)	6 (4)	0.10
60–69	4,726 (25.6)	5 (4)	0.10
70–79	375 (2.0)	0	0
80–	14 (0.1)	0	0
Total	18,539 (100)	22	0.12

1.0 cm or less in diameter as measured by US. The tumor diameter in the 13 non-palpable tumors ranged from 0.6 ×0.5 cm to 2.5×1.2 cm, and 11 of them were overlooked at the physical examinations, one was diagnosed as mastopathy, and one was diagnosed as an induration of the breast.

Age distribution of all examinees and the 27 breast cancer patients detected in the screening Table VI shows the incidence of detection by age decade in the participants screened by both physical and US examination. The highest incidence of detection (0.16%) was seen in examinees aged 40–49 years, followed by those aged 30–49 and 50–69 years.

Sensitivity and specificity of US examination for breast cancer Subjects were limited to 10,722 participants who were periodically examined by US in groups Y and Z. The detection rate of breast cancer was 0.08% (9/10,722). When false-negative cases at the repeat screening using US were defined as those in which advanced breast cancer was detected at the next screening, the sensitivity and specificity of US screening combined with physical examination was 100% (9/9) and 97.7% (10,464/10,713), respectively (Table VII). The numbers of true-positive and false-positive cases were 9 and 249, respectively, and the positive predictive value was 3.5%

Table VII. Sensitivity and Specificity of US Combined with Physical Examination

Periodic screening by US examination	Breast cancer confirmation by ANB[a]		
	Present	Absent	Total
Positive	9	249	258
Negative	0[b]	10,464	10,464
Total	9	10,713	10,722

Sensitivity: 100%, Positive predictive value: 3.5%,
Specificity: 97.7%, Negative predictive value: 100%.
a) ANB: aspiration needle biopsy under US guidance.
b) False-negative cases: defined as advanced breast cancer detected at the next screening.

(9/258). There were no false-negative cases, and the negative predictive value was 100%. The cases of US finding classified C, D, or E were selected as positive cases and aspiration needle biopsy (ANB) under US guidance was performed to rule out or confirm malignancy. False-positive cases were mostly benign lesions, but in which malignancy could not be ruled out. These cases required follow-up for 6 months.

DISCUSSION

Screening using MMG for early detection of carcinoma of the breast offers the two potential benefits of a reduction in breast cancer mortality, due to earlier detection in women aged 50–69 years,[2–5] and an increased potential opportunity to apply breast-conserving treatment because of the improved detection of smaller and earlier-staged carcinomas.[6,7] In women under the age of 50 years, the benefits of such screening are unclear.[5,19,20] In Japan, randomized studies have not been employed and no studies of large MMG or US screening programs have been reported. Physical examination with inspection and palpation at breast cancer screening has been well established for many years and is accepted as a routine part of the physical examination of adult women. The sensitivity of physical examination in mass screening is reported to be low, and the qualitative nature of the diagnosis often lead to false-negatives at the initial screening.[8] No significant improvement in the survival rate attributable to physical examination alone has been demonstrated.[9] Recent trials of mass screening by MMG carried out in women aged 50 years or over demonstrated an improved incidence of detection compared with that by physical examination alone.[10,11] The goal of mass screening is to detect the disease at an early and curable stage and thereby to reduce the mortality due to breast cancer. This study revealed that the incidence of detection of early breast cancer by screening with US was higher than that with physical examination alone.

It is generally reported that the detection rate of breast cancer at mass screening by physical examination is about 0.10% in Japan.[21-23] In our study, the rate in each year ranged from 0.02% to 0.16% (mean rate: 0.08%). The highest rate (0.16%) was seen in 1991. This result should be analyzed in relation to the low rates of detection in 1989 and 1990, since there were three advanced cancers in subjects examined by physical examination in repeat screening in 1991. Thus, we presume that it is possible for prior screening to fail to reveal tumors.

It was reported that the detection rate of breast cancer is higher in outpatients examined at a medical institute than in participants examined at mobile screening units.[24] We think that this result reflects the degree of consciousness of health care of the examinees. In our study, however, we obtained the unexpected result in two groups, examined by US, that the rate was higher in group Y, examined at mobile screening units, than that in group Z, examined at our institute. We attribute this difference to the greater proportion of initial examinees and the smaller proportion of total examinees in group Y compared to those in group Z. In brief, this result is owing mainly to detection of four advanced cancers in initial screening in group Y. National statistics prepared by the Japan Breast Cancer Society indicate that the incidence of detection was 0.18% at initial screening and 0.06% at repeat screening.[25] It has also been reported that qualitative diagnosis at the first screening by physical examination alone was often false-negative.[8] Our study did not reveal a greater incidence of detection at the initial examinations compared to the repeat examinations in the group examined by physical examination alone. We suspect that the carry-over of false-negative cases at the initial screening to the screening in the next year contributed to this effect.

Of the early breast cancer tumors found in the screening program, 16 (7 of them 1.0 cm or less in diameter) were detected by US and 2 by physical examination. It has been reported that in women aged 50 years and over about 50% of all tumors detected in mass screening by physical examination alone are early cancer,[21,22] compared to 73% of those detected by MMG combined with physical examination.[10] Our study suggests that US is also useful in mass screening for detection of early breast cancer.

Non-palpable breast cancer is identified by the observation of microcalcification on mammography, abnormal nipple discharge without mass formation, or detection of a mass only by US or by mammography, but it is not detected by physical examination alone. Twelve of the 13 non-palpable breast cancers in our study were early breast cancer (stage I tumor). Moreover, 5 of them were 1.0 cm or less in diameter. The palpable breast cancer tumors showed more advanced stage than the non-palpable tumors. We presume that these tumors detected by US include interval cancers that would be found by physical examination alone in mass screening.

In discussions of the usefulness of mammographic screening in western countries, there seems to be a general consensus that routine screening every one to two years with MMG and clinical examination can reduce breast cancer mortality by about one-third for women aged 50 years and over, though there is no consensus regarding women aged 40–49 years.[5,19,20] The screening in the latter group may reveal a substantial proportion of breast cancer tumors before they are manifested clinically, but the trials carried out thus far have not indicated a significant reduction in subsequent mortality.[5,19,20,26] Mammographic screening trials in Japan's Miyagi and Tokushima Prefectures revealed an improved detection rate of breast cancer, particularly early breast cancer, in women aged 50 years and over.[10,11] Such trials in Japan in women under that age have not previously been reported. In practice, both the incidence of breast cancer and the incidence according to age differ in Japan and in western countries, with lower incidence and younger peak age of incidence in Japan.[27] In younger women, because of the denser breast tissue, it is difficult to detect a mass by MMG. Moreover, increases in breast cancer risk associated with increased radiographic density have been noted in women aged 40–49 years.[28] However, because the detection of masses by US is not influenced by the density of the breast tissues, it is superior to MMG for the detection of breast cancer masses.[17] It is also accepted that US can detect a palpable cancer that may not be visualized on MMG[13-16] and, with the high resolution equipment available, it should be able to detect smaller, non-palpable cancers not seen even on high-quality MMG.[12] MMG sensitivity is low in radiographically dense breasts, near prostheses, at the breast periphery, in surgically altered breasts, or in breasts of pregnant or lactating women. The results of this study reveal that, with US, early detection of breast cancer is possible in women under the age of 50 years.

In this study, we assumed that false-negative cases would be detected as advanced cancer tumors at the next year's screening in the repeat examinees. Although there were no false-negatve cases, two of the 9 true-positive cases, which were all stage I, had abnormal US findings of a hypoechoic mass and all the others had no abnormal findings at the previous screening. These cases were closely followed up. Strictly speaking, false-negative cases cannot be identified, since the natural history of breast cancer is not yet well understood. Furthermore, breast cancer tumors detected only by microcalcification on MMG were excluded from this study, but there is a possibility that MMG can detect even latent cancer. The results of our study show that US screening has high

sensitivity and specificity, but low positive predictive value. The poor positive predictive value remains problematic.

Nevertheless, the results of this retrospective study suggest that US screening for breast cancer is sensitive and effective for detecting early and non-palpable tumors and may also improve the detection of early breast cancer in women under the age of 50 years. The early detection of breast cancer by MMG should be compared with that by US in further studies.

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