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Improved Detection Rate of Early Breast Cancer in Mass Screening Combined with Mammography

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A cohort study to compare mass screening with and without mammography was conducted in Miyagi Prefecture, Japan in order to establish whether the effectiveness of breast cancer screening would be improved when mammography was combined with physical examination. A trial of mass screening combined with mammography was carried out in 9634 women aged over 50. Lateral imaging of the breast using single-view film mammography was performed at the first stage of mass screening in addition to physical examination of the breast. Results in the trial were compared with those obtained in 35511 age-matched subjects without mammography. Thirty breast cancers were found in the trial with a detection rate of 0.31%, which was much higher than that (0.08%) obtained by physical examination without mammography. In 15 of the 30 patients the breast tumor was not palpated at the first screening, but abnormal findings were detected in the mammography. A higher rate (73%) of early breast cancer was obtained in the screening trial with mammography than that (39%) obtained in the screening with physical examination alone. Mass screening combined with mammography is superior to that without mammography for breast cancer screening, especially for the detection of non-palpable, early breast cancer.

Key words: Breast cancer — Mass screening — Mammography

A great deal of effort has been made to improve surgical and radiotherapeutic techniques as well as chemo-endocrine therapies in the management of breast cancer. The mortality rate from breast cancer, however, still remains high. The early detection of breast cancer is believed to be the best means of reducing this mortality[1–7] and film mammography is available for this purpose.[8–10] It is accepted that the cure rate for patients with breast cancer could be improved significantly if breast cancer could be detected at an early stage.[11, 12]

There has been a rapid increase in mammography utilization in western countries, and increasing numbers of asymptomatic women are undergoing screening procedures.[5, 7, 9, 13] Some randomized trials have demonstrated a reduction in mortality from breast cancer after mass screening.[3, 4] In Japan, however, mass screening for breast cancer basically consists of physical examination of the breasts and the regional lymph nodes, and the detection rate of breast cancer remains low, approximately 0.1%.[14–16] A higher detection rate of early stage breast cancer in women was achieved by mass screening as compared to the rate obtained in patients visiting outpatient clinics. However, no reduction in mortality at ten years after surgery was found in breast cancer patients detected by mass screening when compared to the mortality at ten years after surgery obtained in outpatient clinics in Japan.[16]

Mass screening for breast cancer has been conducted in Miyagi Prefecture since 1977.[14] With more than 15 years of experience, we have achieved a detection rate of approximately 0.1% by means of physical examination of the breasts and the regional lymph nodes in combination with cytology of nipple discharge at the first stage of mass screening.

To improve the detection rate of breast cancer at the early stage, a film mammography has been combined with physical examination in the mass screening. Results in the trial were compared with those in age-matched controls obtained by the conventional mass screening without using mammography. The current study was initiated to establish whether or not the effectiveness of breast cancer screening would be improved by the screening with mammography.

SUBJECTS AND METHODS

Subjects From December 1989 to November 1991 9634 women aged over 50 in 32 communities registered for the trial of physical examination (PE) combined with film mammography (MG) at the first stage of mass screening

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for breast cancer. Controls were 35511 age-matched women in another 27 communities. The latter group participated in conventional screening as described below without MG.

Mass screening The conventional first stage mass screening for breast cancer detection was conducted as follows. The first screening consisted of PE, e.g., inspection and palpation, of the breasts and the regional lymph nodes by a well-trained surgeon. Smear cytology was also performed for the nipple discharge. The subjects with any abnormal findings detected by PE, and those with abnormal cytologic features (class II to V) entered the second stage of screening with film MG and ultrasonography. The women requiring aspiration biopsy cytology and surgical biopsy were referred to community hospitals, whereas the subjects in need of further examination were followed up at the Breast Cancer Detection Center, the Miyagi Cancer Society. The subjects without any findings were re-examined every 2 years.

In this trial, lateral imaging of both breasts using MG was performed on women aged over 50 years in addition to PE at the first stage of mass screening. The MG was evaluated at the screening after the PE. Afterwards, the mammographic findings were also evaluated by another two physicians without knowledge of the results of PE at the Breast Cancer Detection Center. The screenees having abnormal findings in either MG or PE entered the second stage of screening where they received further examinations including ultrasonography and two views of the breasts by MG. Results in the trial were compared with those obtained by conventional screening without MG.

Scoring method for mammographic findings To evaluate mammographic findings a scoring system was employed in the trial. Tumor masses and calcification are the major two characteristics indicating breast tumor in MG. To assess the findings as benign or malignant, tumor masses were evaluated according to the shape, margin, size and location of the lesion, and associated findings such as skin changes and calcification. Calcification was evaluated according to the type, size, number, distribution, and associated findings such as tumor masses. We divided the mammographic findings into 5 grades in each of the two characteristics, e.g., 0: no finding, 1: benign, 2: benign, but malignancy not ruled out, 3: malignancy suspected, and 4: malignancy. This scheme is basically in accordance with the breast imaging criteria of Kopans.[17] The score 0 indicates negative MG without any mass or calcification. The score 1 indicates benign findings, with no suggestion of cancer. The score 2 indicates probably benign, but cancer not ruled out. There are radiographic characteristics such as mass lesions with well-demarcated margins or small clustered calcification with round shape. The score 3 implies suspicion of malignancy, for which biopsy is recommended, and the score 4 indicates malignant lesion with characteristics such as mass with spicular formation, or microcalcification.

The mammographic score, 0 to 4, was taken to be the highest grade among all the characteristics. The subjects showing the score 2 or more in the MG were taken to the second stage of screening. The second screening consisted of two different views of MG (cranio-caudal as well as lateral) and ultrasonography together with careful physical examination of the breasts and the regional lymph nodes.

RESULTS

Breast cancer detection in mass screening with MG As shown in Table I, no abnormal finding (score 0) was obtained in the MG of 7143 women, and benign characteristics (score 1) were found in 2316 screenees. Thus, the vast majority (98.2%) of the subjects were considered to be free of malignancy. Mammographic characteristics of score 2 (benign lesions, but malignancy not ruled out) were found in 151 women, those of score 3 (suspected malignancy) were found in 14 women and those of malignancy (score 4) were detected in 10 women. Only 1.8% of the subjects had the score 2 or more in the MG and were subjected to further screening. Breast cancer was found in 29 of these 175 subjects (16.5%) after the second stage of screening. The detection rates increased as the scores increased. A breast mass was defined by the PE, but not by the MG in one breast cancer patient. Biopsy of the breast mass proved it to be breast cancer two months after the first stage of screening. The simultaneous MG at the first screening demonstrated microcalcification of benign characteristics with a mammographic score of 1. Therefore, 30 breast cancers were detected in the trial using the system of PE combined with MG, with the detection rate of 0.31%.

Table I. Breast Cancer Detection Rates Based on Mammographic Diagnosis in Mass Screening Combined with Mammography

Mammographic diagnosis[a]	Number of subjects (%)[b]	Number of breast cancers	Detection rate (%)
0	7143 (74.1)	0	0
1	2316 (24.1)	1	0.04
2	151 (1.6)	13	8.6
3	14 (0.1)	6	42.9
4	10 (0.1)	10	100
Total	9634 (100)	30	0.31

a) 0: no findings, 1: benign, 2: benign, but malignancy not ruled out, 3: malignancy suspected, 4: malignancy.
b) Proportion of subjects.

Table II. Breast Cancer Detection Rates Based on Age Distribution According to Screening Systems

Age distribution	PE and MG combined			PE alone		
	Number of subjects (%)[a]	Number of breast cancers	Detection rate (%)	Number of subjects (%)[a]	Number of breast cancers	Detection rate (%)
50–54	2740 (28.4)	3	0.11	9728 (27.4)	7	0.07
55–59	2885 (29.9)	6	0.21	10437 (29.4)	6	0.06
60–64	2299 (23.9)	13	0.57	8885 (25.0)	7	0.08
65–69	1203 (12.5)	6	0.50	4585 (12.9)	5	0.11
70–74	417 (4.3)	2	0.48	1503 (4.2)	2	0.13
75–	82 (0.9)	0	0.00	373 (1.0)	1	0.26
All age	9634 (100)	30	0.31	35511 (100)	28	0.08

PE, physical examination; MG, mammography.
a) Proportion of subjects.

Table III. Breast Cancer Detection Rates Based on Mass Screening Histories of the Subjects

History of subjects	PE and MG combined			PE alone		
	Number of subjects (%)[a]	Number of breast cancers	Detection rate (%)	Number of subjects (%)[a]	Number of breast cancers	Detection rate (%)
For the first time	2288 (23.7)	11	0.48	6227 (17.5)	11	0.18
On and after the second time	7355 (76.3)	19	0.24	29284 (82.5)	17	0.06
Total	9634 (100)	30	0.31	35511 (100)	28	0.08

PE, physical examination; MG, mammography.
a) Proportion of subjects.

Among the 30 patients, 14 were detected by both PE and MG, 15 were detected by MG only, and the other one was defined by PE only.

Breast cancer detection based on age distribution Table II shows the breast cancer detection rates according to age distribution of the screenees at 5-year intervals over 50. The two screening systems were applied to the age-matched subjects. As compared to the control subjects, higher detection rates were obtained in the trial subjects aged from 50 to 74 years old. Approximately fourfold higher breast cancer detection rates were obtained in women aged over 60 who participated in the screening trial of PE combined with MG, as compared to the detection rates obtained in the control subjects at the same age distribution.

Breast cancer detection rates based on mass screening histories of the subjects There was no statistically significant difference between the proportion of subjects with previous mass screening histories who registered for the trial and that of control subjects with such histories (Table III). Although the subjects receiving screening for the first time demonstrated higher detection rates than the subjects on and after the second time in both groups, approximately fourfold higher detection rate was obtained in the trial group with the combined system, as compared to that in the control group with PE alone.

Non-palpable breast cancers detected by MG Breast tumor was not palpated in 15 of the 30 breast cancers (50%), but was detected by MG. Among the 15 breast cancers, 3 patients showed a mammographic finding indicating breast cancer (score 4), 6 showed the finding of possible breast cancer (score 3), and 6 had benign characteristics, but with malignancy not ruled out (score 2). Histopathological examination revealed that 5 of the 15 were intraductal carcinomas, in which microcalcification was the only finding detected by MG. No carcinoma metastasis to the regional lymph nodes was found in the surgically resected specimens of the 15 patients.

Breast cancer detection and clinical stage Clinical stage of breast cancer was compared between the patients defined in mass screening combined with MG and those with PE alone (Table IV, UICC Classification). As stated above, breast tumor was not palpated in 15 patients including 5 intraductal carcinomas (Tis=stage 0) in the trial group. The 10 cancers other than intraductal carcinomas were first considered to be T0 without lymph node metastasis, but these 10 patients were classified into stage I breast cancers by mammographic imaging accord-

Table IV. Stage Grouping (UICC) of Breast Cancers Detected by the Two Mass Screening Systems

Screening system	Number of breast cancers (%)					
	Stage 0	Stage I	Stage II	Stage III	Stage IV	Total
PE and MG combined	5 (17)	17 (57)	5 (17)	3 (10)	0 (0)	30 (100)
PE alone	2 (7)	9 (32)	16 (57)	1 (4)	0 (0)	28 (100)

PE, physical examination; MG, mammography.

Table V. Sensitivity and Specificity of the Two Screening Systems Obtained after 2 Years of Follow-up

Screening	PE and MG combined			PE alone		
	Breast cancer			Breast cancer		
	Present	Absent	Total	Present	Absent	Total
Positive	14	151	165	10	769	779
Negative	0	4765	4765	4	14820	14824
Total	14	4916	4930	14	15589	15603
Sensitivity		100%			71.4%	
Specificity		96.9%			95.1%	

PE, physical examination; MG, mammography.

ing to the UICC rules. The 5 patients with intraductal carcinoma detected by the MG did not exhibit any lump. The stage of the patient whose breast mass was detected only by PE, but not by MG was classified as stage I, and 5 other patients with stage I were detected by both PE and MG. Therefore, 17 of the 30 patients (57%) in the trial group were classified as stage I. A higher rate (73%) of early breast cancer (stage 0 plus stage I) was acquired in the trial group using MG, as compared to that (39%) in the control group without MG.

More than half (61%) of the breast cancers detected by PE alone were cancers at clinical stages II and III, whereas only 27% of the breast cancers detected by PE with MG were cancers at clinical stages II and III.

Sensitivity and specificity of mass screening combined with MG in comparison to those of PE alone Since the study was conducted from December, 1989 to November, 1991 for 2 years, we evaluated the sensitivity and specificity of this trial by following the first half (December, 1989 to November, 1990) of the screenees for two years. During December, 1989 to November, 1990 4930 screenees registered in the combined system, whereas 15589 screenees participated in the screening system with PE alone (Table V). Numbers of the subjects who were positive or negative in each screening are listed according to the presence of breast cancer identified by the screening. Four women screened by PE alone subsequently developed breast cancer, but none of the women screened by the combined system developed breast cancer for 2 years. As shown in Table V higher values of sensitivity and specificity were obtained by the screening system in which PE and MG were combined, than those obtained by the system with PE alone.

DISCUSSION

This is the first cohort trial of mass screening combined with MG to show an increased detection rate of early breast cancer in Japan. The Health Insurance Plan of New York (HIP) study has demonstrated in a randomized trial a reduction in mortality from breast cancer after mass screening.[3,4] In Japan, however, mass screening for breast cancer has been sporadically conducted by the suggestion of the Ministry of Health and Welfare, and it is now impossible to carry out a randomized trial for breast cancer screening. In the cohort trial we used a single view MG in addition to PE for women aged over 50 years, and compared the results with those obtained by PE without MG in age-matched controls at the first stage of mass screening.

Thirty breast cancers were found in the trial, corresponding to a detection rate of 0.31%, which was much higher than that (0.08%) obtained by the screening with PE alone. In 15 of the 30 breast cancer patients the tumor was not palpated at the screening, but abnormal findings were detected in the screening MG. On the other hand, one breast cancer was detected by PE, but not by MG in the combined screening. On the basis of TNM classifica-

tion (UICC), a higher rate (73%) of early breast cancer was obtained in the trial combined with MG than that (39%) obtained by PE alone. These results indicate that the PE combined with MG is an appropriate system for breast cancer screening, especially for detection of non-palpable, early breast cancer.

Cancer detection rate can be influenced by cancer prevalence among the screenees, however, and we should have compared the results obtained by PE and MG with the results by PE alone within the population of the combined group (9634 women). It is not appropriate in the combined group, however, to assess the data by separating the results of PE from those obtained by MG, because the screenees in this trial received PE and MG simultaneously at the first stage of screening. To compare the detection rate by PE alone with that by MG alone a new screening system has been conducted from April, 1992, in which mammographic assessment is completely separated from assessment by PE at the first stage of screening.

A computer-based mathematical model for projecting cancer incidence and mortality in the presence of cancer control programs was proposed by Levin *et al.*[11] In the model, women aged 50 to 70 are offered the HIP screening package (breast physical examination and mammography), two-thirds avail themselves of the offer, and 95% of those with positive results continue to a workup. Stage distribution of early breast cancer shifts from 17% in the non-screened group to 75% in the new trial group, and a 30% reduction in mortality from breast cancer is estimated for the women after 15 years of follow-up, although there is some indication from the HIP study that the women screened have a higher relative risk of breast cancer than the unscreened population. Early treatment of breast cancer may not influence the chance of recovery, but may merely postpone death due to breast cancer. Longer follow-up of the breast cancer patients detected in our study is necessary to determine the effect of screening on cancer mortality.

It is difficult to evaluate quantitatively the mammographic findings. We employed a scoring system for mammographic diagnosis on the screening program in which two well trained physicians viewed the MG and tried to evaluate the findings according to the 5 grade scores in respect of malignancy without knowledge of the result of PE. The women with score 2 or more were offered the second stage of screening. The higher the score estimated in the MG, the higher the detection rate obtained after the second stage of screening (Table I). It should be noted that women with the score 0 or 1 were not offered the second stage of screening, and a careful follow-up of the subjects would be required. As a matter of fact, one breast cancer was not detected by MG though the score was estimated to be 1. A proper quality assurance program for MG is also necessary to optimize the benefits of early detection of breast cancer through screening. Such a quality assurance program includes not only the quality control of equipment and processing, but also the training and monitoring of performance of physicians and technologists.

We have calculated the sensitivity and specificity of the two screening tests by following the examinees for two years. The sensitivity and specificity of the test by PE alone were almost the same as those in Osaka reported by Ota *et al.*[18] The sensitivity and specificity of the test using PE combined with MG, however, were higher than those obtained by PE without MG conducted either in Miyagi or in Osaka, suggesting that the screening combined with MG is a better system than the screening with PE alone for the detection of breast cancer.

Cancer detection rate and stage distribution are not the only factors relevant to deciding whether PE combined with MG is worthwhile for nationwide mass screening for breast cancer. The planning of cancer control programs is a complex task. A suitable model, which offers an approach to evaluating public health programs in breast cancer control, should be established as an aid to the decision-making process.

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