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Comparison of False Negative Rates among Breast Cancer Screening Modalities with or without Mammography: Miyagi Trial

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False negative rates were compared in two screening modalities, physical examination with or without mammography, in an intervention study for women aged over 50 in Miyagi Prefecture. Thirty-five breast cancers were detected in 12,515 subjects who participated in the trial consisting of physical examination and mammography, whereas 44 breast cancers were detected in 50,105 subjects who received physical examination alone, so that the detection rates were 0.28% and 0.09%, respectively. Among 50,061 subjects who received physical examination alone, 8 women were diagnosed as having breast cancer within 12 months after the screening, while only one of 12,480 screenees receiving the combined modality was so diagnosed, implying false negative rates of 15.4% and 2.8%, respectively. When the screening sensitivity in the combined system was analyzed according to each single modality, the false negative rate provided by physical examination with mammography turned out to be 2.8%, significantly lower than that (33.3%) by the physical examination alone. Minimal breast cancers represented 25.7% of all screen-detected cancers in the combined modality, compared with 9.1% in the modality without mammography. The trial thus indicates that physical examination combined with mammography may be an appropriate modality for breast cancer screening in women aged over 50 on the basis of screening sensitivity.

Key words: Breast cancer screening — False negative rate — Mammography — Screening sensitivity

The past year has been a confusing one for women and physicians in Japan regarding recommendations for breast cancer screening. In 1987, a research group (Project No. 62-34) was organized to evaluate the feasibility of mass screening for breast cancer with a Grant-in-Aid from the Ministry of Health and Welfare, Japan. In 1989, Ota *et al.* presented the group's results showing no reduced mortality at ten years after surgery in breast cancer patients detected by mass screening when compared to the mortality in outpatients.[1)]

A randomized controlled study to examine the effectiveness of breast cancer screening has not been conducted in Japan. Today, it is impossible to conduct such a study, since mass screening for breast cancer is now nationwide. The effectiveness of cancer screening can be evaluated in terms of mortality reduction in a case-control study, but this requires long-term follow-up of screen-detected breast cancer patients. Statistical analysis of parameters other than mortality reduction, however, may be useful to estimate the efficacy of mass screening, because the impact on mortality will be greater if the screening sensitivity is adequate.[2)]

The simplest procedure is to estimate the relative sensitivities of modalities used in combination, taking all screen-detected cancers and interval cancers as the denominator. The traditional method takes account of interval cancers presenting with symptoms during the 12-month period before the next screen is due, and assumes that these are the false negatives of the previous screen. Relative sensitivity is defined as the proportion of screen-detected cancers in the sum of screen-detected and interval cancers. In the combined screen, the false negative rate of each modality is defined as the proportion of interval cancers in 12 months after screening and cancers detected only by the other modality at the screening out of the sum of interval cancers and all screen-detected cancers.

We have recently described an improved detection rate of early breast cancer in mass screening combined with mammography as compared to the rate obtained by physical examination alone.[3)] This study was conducted to evaluate the efficacy of breast cancer screening combined with mammography, based on false negative rates. Furthermore, rates of minimal cancer (defined as all invasive cancers smaller than 1 cm and all *in situ* cancers) were compared among the breast cancers detected by different screening modalities, as it has been well established that smaller lesions with no histologic evidence of axillary metastasis have the best prognosis.[4)]

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SUBJECTS AND METHODS

Subjects The trial was carried out on women aged over 50 from December, 1989 to June, 1992 in Miyagi Prefecture. During this period a screening modality combining physical examination with mammography was employed on 12,515 women in 34 municipalities, whereas a screening modality with only physical examination was employed on 50,105 women in 25 municipalities as a control.

Screening modality: physical examination alone The conventional first-stage screening consisted of physical examination, e.g., inspection and palpation, of the breasts and the regional lymph nodes. Smear cytology was performed on the subjects with abnormal nipple discharge. The subjects with any abnormal findings detected by the physical examination, and those with abnormal cytologic features (class II to V) entered the second stage of screening with film mammography 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 subsequently followed up at the Cancer Detection Center, Miyagi Cancer Society.

Screening modality: physical examination combined with mammography In the trial, imaging mammography was performed at the first stage of mass screening in addition to physical examination. First, the subjects were screened by physical examination as described above without any information on mammography. Thereafter, physicians reviewed the mammograms for each subject. The diagnosis based on physical examination and that based on mammography are autonomously presented. The mammographic technique was a single lateral view of each breast. The mammographic findings were afterward reviewed by another two physicians at the Cancer Detection Center, Miyagi Cancer Society. The results were compared with those obtained by the conventional mass screening without mammography.

We used the municipal mobile mammography unit at the first stage of breast cancer screening. Therefore, the mammography equipment was the same throughout the trial. The individual physicians' experience was consistent between the modality of physical examination with mammography and the modality of physical examination alone.

Classification of mammographic findings The classification for mammographic findings was as previously described.[3] In brief, the mammographic findings were classified into 5 grades in three categories, i.e., tumor shadow, microcalcification, and findings associated with breast cancer, based on malignant potential from class I to class V; i.e., class I: no finding, class II: benign, class III: benign but malignancy not ruled out, class IV: malignancy suspected, and class V: malignancy. The mammographic classification was taken as the highest grade among the characteristics. The subjects showing class III or more in the mammography were passed to the second stage of screening. The second screening consisted of two different views of film mammography (cranio-caudal as well as lateral views) and ultrasonography together with careful physical examination of the breasts and the regional lymph nodes.

Definition of false negative rate in breast cancer screening False negative was defined as an interval breast cancer in the 12 months after screening. Breast cancer detected by the other screening modality performed at the same screening was also considered a false negative. Therefore, the false negative rate was defined as the proportion of interval cancers in 12 months after screening and cancers detected only by the other modality at the screening out of the sum of interval cancers and all screen-detected cancers. The subjects who required further examination for malignancy after the first stage of screening were seen at community hospitals, or at the Cancer Detection Center, Miyagi Cancer Society. The subjects who did not require further examination at the first stage screening were carefully followed up at their respective municipalities and community hospitals. We obtained information on subjects diagnosed as having interval breast cancer from the municipality where the subject was living.

Statistical analysis The chi-square test was applied for statistical analysis of the data.

RESULTS

Comparison of screening modalities based on positive screening rate, detection rate, sensitivity, false negative rate and specificity The positive rate for the screening test (defined here as the rate of screen-positive subjects who were recalled for further examination), breast cancer detection rate, sensitivity, false negative rate and specificity of the two screening modalities are shown in Table I. The positive screening rate in the combined system was 3.58%, lower than that of physical examination alone, indicating that more subjects receiving the combined screening did not require further examination by physicians to exclude the possibility of breast cancer, as compared to the subjects receiving only physical examination. Thirty-five breast cancers were detected in 12,515 subjects who participated in the trial with mammography, whereas 44 breast cancers were detected in 50,105 subjects who received the conventional physical examination without mammography, so that the detection rates of breast cancer were 0.28%, and 0.09%, respectively. The detection rate obtained by the combined system was significantly higher than that provided by physical examination alone ($P < 0.01$).

Among the 50,061 subjects who received physical examination, 8 women were subsequently diagnosed as having breast cancer within 12 months after the screening, while only one among the 12,480 screenees who participated in the combined modality was diagnosed as having breast cancer. The sensitivity, defined as the proportion of screen-detected cancers out of the sum of screen-detected and interval cancers, was 97.2% in the combined system, whereas it was 84.6% with the physical examination alone. The false negative rate of the combined modality was 2.8%, much lower than that in the system without mammography. As another measure of sensitivity, only 2.8% of breast cancers in the combined trial were found between annual follow-ups, compared with 15.4% in the control group without mammography.

Among the 8 patients, who were diagnosed as having interval breast cancers in the 12 months after the screening with physical examination alone, 5 were classified into clinical stage II, 2 were stage I, and the other was stage III according to the TNM classification. The one interval cancer patient, who had participated in the screening with mammography, was classified into clinical stage I.

Physical examination combined with mammography As shown in Table II the screening sensitivity in the system consisting of physical examination and mammography was analyzed according to each modality separately. The positive rate for mammography was 1.84%, much less than that (3.15%) for physical examination. One patient was diagnosed as having an interval breast cancer 12 months after the screening. Eleven patients with breast cancer were detected by mammography alone, whereas 2 patients were detected by physical examination alone. Therefore, the false negative in physical examination and that in mammography amounted to 12 and 3, resulting in false negative rates of 33.3% and 8.3%, respectively. The false negative rate (2.8%) provided by the combined

Table I. Comparison of Positive Rate for Screening Test, Detection Rate, Sensitivity, False Negative Rate and Specificity of Screening Modalities with or without Mammography

Screening modality	PE with MG			PE alone		
	Breast cancer			Breast cancer		
	Present	Absent	Total	Present	Absent	Total
Positive	35	413	448	44	2196	2240
Negative	1	12066	12067	8	47857	47865
Total	36	12479	12515	52	50053	50105
Positive rate (%)		3.58			4.47	
Detection rate (%)		0.28[a)]			0.09	
Sensitivity (%)		97.2			84.6	
False negative rate (%)		2.8			15.4	
Specificity (%)		96.7			95.6	

PE, physical examination; MG, mammography.
a) Significant difference from the physical examination alone group ($P<0.01$).

Table II. Positive Rate for Screening Test, Detection Rate, Sensitivity, False Negative Rate and Specificity of the Screening Modality which Combined Physical Examination with Mammography

Screening modality	Physical examination			Mammography			Combined		
	Breast cancer			Breast cancer			Breast cancer		
	Present	Absent	Total	Present	Absent	Total	Present	Absent	Total
Positive	24	370	394	33	197	230	35	413	448
Negative	12	12109	12121	3	12282	12285	1	12066	12067
Total	36	12479	12515	36	12479	12515	36	12479	12515
Positive rate (%)		3.15			1.84			3.58	
Detection rate (%)		0.19			0.26			0.28[a)]	
Sensitivity (%)		66.7			91.7			97.2	
False negative rate (%)		33.3			8.3[b)]			2.8[c)]	
Specificity (%)		97.0			98.4			96.7	

a)–*c*) Significant difference from the physical examination group ($P<0.01$).

Table III. Breast Cancer Detection Rates by the Two Screening Modalities According to Mass Screening Histories of the Subjects

History	PE with MG			PE alone		
	No. of subjects	No. of breast cancers	Detection rate (%)	No. of subjects	No. of breast cancers	Detection rate (%)
Initial	2838	12	0.42	8043	14	0.17
On and after second time	9646	23	0.24	42062	30	0.07

PE, physical examination; MG, mammography.

method was significantly lower than that by the physical examination alone ($P<0.01$). The detection rate of breast cancer by physical examination was 0.19%, much higher than that obtained by physical examination alone conducted in other municipalities (Table I). It should be emphasized here that a detection rate bias might not be excluded since the physical examination was conducted at the same time as mammography at the screening sites.

Breast cancer detection rates according to mass screening history Mass screening history may influence the breast cancer detection rate. Among 12,515 screenees in the trial, 2,838 women had no history of breast cancer screening, and another 9,646 had already received breast cancer screening with the conventional physical examination. The detection rate was 0.42% in the initial screening, whereas it was 0.24% in the screenees who had had previous mass screening (Table III). Compared to the detection rates obtained by physical examination alone, both the rate of initial screening, and the rate on and after the second time were shown to be higher: 0.42% versus 0.17%, and 0.24% versus 0.07%, respectively.

Minimal breast cancers Minimal breast cancers were defined as all invasive cancers smaller than 1 cm without lymph node metastasis and all intraductal and *in situ* cancers. Minimal breast cancers represented 25.7% (9 of 35) of all screen-detected cancers in the trial with mammography, compared with 9.1% (4 of 44) in the control group (Table IV). Among the 9 minimal cancers, 7 (78%) were defined by mammography alone, 2 (22%) were detected by both modalities, but none was detected by physical examination alone.

Table IV. Rates of Minimal Breast Cancers Obtained in the Two Screening Modalities

	No. of breast cancers	No. of minimal cancers	%
PE with MG	35	9	25.7
PE alone	44	4	9.1

PE, physical examination; MG, mammography.

DISCUSSION

We estimated the relative sensitivities and false negative rates of screening modalities to define the effect of combining mammography with physical examination. A lower false negative rate was obtained in the combined screening modality, compared with that found in physical examination alone.

There has been a marked increase in mammography utilization in western countries, and increasing numbers of asymptomatic women are undergoing screening procedures.[5-12] Some randomized trials have demonstrated a reduction in mortality from breast cancer after mass screening.[5,6,8] In a randomized trial conducted by the Health Insurance Plan of New York (HIP) from 1963 to 1970, a 50% reduction in breast cancer mortality was demonstrated among study group women aged 50 years and older at the time of entry.[5,6] The Breast Cancer Detection Demonstration Project (BCDDP), a non-randomized trial in which women were screened with mammography and physical examination from 1973 to 1981, demonstrated a 58% reduction in breast cancer mortality from initial screening of women aged 50 and older.[7] The Swedish two-county trial, a randomized trial in which only a single medio-lateral oblique view mammogram was conducted, in 1977, also achieved 40% reduction in breast cancer deaths in the 50–74 year age group at the initial 7-year follow-up.[8] Mammography seems to be an essential adjunct for breast cancer screening, at least for women aged 50 and older.[12,13]

In Japan, however, a mortality reduction in breast cancer has not been demonstrated in clinical trials using mammography conducted at the first stage of mass screening. We have recently described an improved detection rate of breast cancer when women aged over 50 were screened with physical examination and mammography, as compared to the result obtained by the conventional physical examination alone.[3] In that trial we used single-view mammography in addition to physical examination for women aged over 50 years old, and compared the results with those in age-matched controls subjected to physical examination without mammography at

the first stage of mass screening. The trial was conducted in 1989, and it is too early to estimate the reduction in breast cancer deaths among the women screened.

It is possible to evaluate the effectiveness of the screening modality by comparing sensitivity data obtained in the trial with those obtained in other trials, such as HIP and BCDDP trials. The first point to be evaluated is interval cancer, or false negative rate. The interval cancer rate obtained in the Miyagi trial was 2.8%, which is very much lower than the rate, 9.2%, in the HIP trial[14] or that, 7.8%, in the BCDDP trial,[15] indicating improved sensitivity in the Miyagi trial.

As another measure of screening sensitivity, the rate of minimal cancer (defined here as all invasive cancers less than 1 cm in diameter and *in situ* cancers) was increased in the trial, when compared to the rate obtained in the control group. The minimal cancers represented 25.7% of all screen-detected cancers in the trial, compared with 8.0% in the HIP study, and 25.0% in the BCDDP study.[16] This result again suggests the effectiveness of the trial, since breast cancer patients with minimal tumor and without lymph node involvement have been shown to have a better prognosis than other patients.[4, 17]

The time taken for a reduction in breast cancer mortality to appear will depend on the initial quality of the screening modalities used. The level of effect in the target population will be strongly dependent on the degree of compliance and on the quality of the mammography. In the BCDDP trial, in which newer mammography methods were used, the detection rate was approximately twice those found in the HIP study: 0.55% versus 0.27% on initial screening and 0.26% versus 0.15% at the second annual examination.[14, 15] When the detection rate and the minimal breast cancer rate of the Miyagi trial are compared with those obtained in the HIP and BCDDP trials, the Miyagi trial, in which modern mammographic methods were used, achieved a higher level of effect in the target population aged 50 and older.

Physical examination, for women over 50, has lower sensitivity than mammography, and in some studies was inferior to mammography in specificity and predictive value.[18, 19] In programs with high-quality mammography, physical examination may not be a cost-effective adjunct to mammography for screening. The cost-effectiveness of screening every 2–3 years by mammography for subjects of age 50–70 compares well with that of many other medical procedures. We are now conducting a further trial to compare the effect of mammography alone with that of physical examination alone for breast cancer screening in women aged 50–70.

Screening for breast cancer by mammography every 1 to 3 years can reduce breast cancer mortality in women age 50–70.[12–14] In women in their forties there is little evidence of benefit, at least in the first 10 years after screening is initiated, except for the BCDDP trial, in which 71% mortality reduction has been estimated from initial screening of women younger than 50 years.[16, 20, 21] In Miyagi Prefecture, we are also looking at the effectiveness of physical examination combined with mammography for breast cancer screening in women aged 40–49.

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