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Mass Screening for Breast Cancer: Comparison of the Clinical Stages and Prognosis of Breast Cancer Detected by Mass Screening and in Out-patient Clinics

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To establish the criteria for assessing the life-prolonging effect of mass screening for breast cancer, clinical stage and prognosis of breast cancer detected by mass screening in 11 regions of Japan were compared with those for matched patients in out-patient clinics. A total of 728 patients detected by mass screening and 1,450 found in the out-patient clinics were reviewed. The stage of the disease was Tis or I in 40.9% of the patients detected by mass screening, and 28.7% of those found in the out-patient clinics. In contrast, stage III was found in 9.3% and 14.6%, respectively, indicating that early stages were significantly more common in the patients detected by mass screening. The overall survival curve for the patients detected by mass screening was compared with that for those found in the out-patient clinics. The 5-year survival rate was significantly higher in the patients detected by mass screening (91.7% vs. 85.6%; $P<0.01$), while the 10-year survival rate was slightly higher in the same group of patients, but the difference from the other group was not significant (80.5% vs. 78.1%). Women who had conducted breast self-examination (BSE) showed a higher survival rate than those who had not conducted BSE.

Key words: Breast cancer — Mass screening — Early detection — Matched pair analysis — Breast self-examination

The incidence of breast cancer has been increasing in Japan, and this cancer is expected to become the No. 1 killer in Japanese women by the year 2,000. Some 10 years ago, mass screening for breast cancer was conducted in only a few hospitals, but today it is nationwide.[1)] Health authorities and researchers are keen to proceed with the program for mass screening of breast cancer, and a research team on breast cancer screening was set up in 1987 (Project No. 62-34) as one of the cancer research projects sponsored by the Ministry of Health and Welfare. This seems to be of the utmost importance for secondary prevention of breast cancer; in other words, early detection and treatment of breast cancer require an efficient method for screening for breast cancer, and the life-prolonging effect of the mass screening must be accurately estimated. For this purpose, it is valuable to compare clinical stage and prognosis of breast cancer detected by mass screening with those of breast cancer found in out-patient clinics.

In the present study we investigated and compared clinical stage and prognosis of patients with breast cancer detected by mass screening in 11 regions of Japan with those found in out-patient clinics. The two groups of patients were matched for age and the time of treatment in each hospital.

SUBJECTS AND METHODS

In 1987, a research group (with Dr. Tominaga as the chairman) was organized to study the feasibility of mass screening for breast cancer with a Grant-in-Aid from the Ministry of Health and Welfare. The members of this

research group compared the progress and survival of patients with breast cancer detected by mass screening in their regions with those of patients found in their out-patient clinics.

Two matched patients were selected from those found in out-patient clinics to have breast cancer, for each patient detected in mass screening, according to the following criteria:

Criteria 1) First, patients who were found to have breast cancer by mass screening were selected for the study. 2) Second, two matched patients with breast cancer detected in out-patient clinics, were selected for each patient from mass screening so that the following factors matched.

Priority in matching 1) Patients treated in the same hospital. 2) Patients of similar age: Date of birth was within 5 years of the date of birth of the patient detected in mass screening. 3) Patients who underwent an operation (or began treatment) on the days closest to the date of detection by mass screening (two patients for each one found by mass screening, one found before the detection in mass screening, and the other after the detection).

The following 14 factors were recorded for each patient: name of hospital, name of patient, date of birth, date of operation (or first treatment), date of first visit to the clinic, date of established diagnosis, awareness of symptoms (if aware, why she noticed them), the history of mass screening, treatment used (surgery, chemotherapy, etc.), stage of the disease (according to the new TNM classification system approved in 1972, and confirmed in 1978), size and histology of the tumor, classification of lymph node metastases by histological evidence (n classification), and last date of confirmed survival, or date of death (together with the cause). Histology of the tumor, and n classification were evaluated according to the general rules for clinical and pathological records of mammary cancer of the Japan Mammary Cancer Society.

Statistical analysis was conducted by use of the χ^2 test, and life table analysis was done by the actuarial method.[2] Significance testing was done based on standard errors of cumulative survival rates estimated by Greenwood's formula.

In most regions which participated in the present study, the primary screening was conducted by interview and inspection and palpation of the breasts by physicians. As necessary, secondary examinations by mammography, ultrasonography or aspiration biopsy were also used.

RESULTS

Clinical stages and histological findings Patients with breast cancer were gathered for the present study in the 11 regions shown in Table I. A total of 728 patients detected by mass screening (patients who underwent mass screening, and were found to have breast cancer) and 1,450 found in the out-patient clinics (patients who visited out-patient clinics, and were found to have breast cancer) were reviewed. Mean age ($\pm$SD) was 49.0 ($\pm$9.9) years in mass screening and 48.9 ($\pm$9.9) in out-patient clinics.

Table II shows the clinical stage of the patients detected by mass screening and in the out-patient clinics. The clinical stage of the disease was Tis or I in 40.9% of the patients detected by mass screening, and 28.7% of those found in the out-patient clinics. In contrast, stage III was found in 9.3% and 14.6%, respectively, indicating that early stages were significantly more common in

Table I. Study Regions and the Number of Breast Cancers Detected by Mass Screening and in Out-patient Clinics

Region	(Researcher)	Number of hospitals	Number of breast cancers	
			Mass screening	Out-patient clinic
Hokkaido	(Ogita)	1	123	246
Miyagi	(Abe/Yoshida)	3	98	190
Tochigi	(Honda)	1	1	2
Gunma	(Ishida)	7	123	246
Tokyo	(Enomoto)	1	28	56
Aichi	(Kido)	1	2	4
Gifu	(Kashiki)	1	8	16
Osaka	(Taguchi/Ota)	1	129	258
Tokushima	(Morimoto)	1	85	170
Kochi	(Itoh)	1	104	208
Fukuoka	(Tashiro)	1	27	54
Total		19	728	1,450

Table II. Clinical Stage of the Breast Cancer Patients Detected by Mass Screening and in Out-patient Clinics

	No. of subjects (%)	
	Mass screening	Out-patient clinics
Stage grouping		
Tis	59 (8.1)	49 (3.4)**
I	239 (32.8)	367 (25.3)**
II	352 (48.4)	791 (54.6)**
III	68 (9.3)	211 (14.6)**
IV	9 (1.2)	27 (1.9)
Unknown	1 (0.1)	5 (0.3)
Total	728 (100.0)	1,450 (100.0)
T-primary tumor		
Tis, T0	33 (4.5)	36 (2.5)*
T1	249 (34.2)	394 (27.2)**
T2	342 (47.0)	789 (54.4)**
T3	35 (4.8)	100 (6.9)
T4	26 (3.6)	112 (7.7)**
Unknown	43 (5.9)	19 (1.3)**
N-regional lymph nodes (macroscopic)		
N0	288 (39.6)	531 (36.6)
N1	368 (50.5)	806 (55.6)*
N2	26 (3.6)	63 (4.3)
N3	2 (0.3)	28 (1.9)**
Unknown	44 (6.0)	22 (1.5)**
n-regional lymph nodes (histological)		
n0	460 (63.2)	817 (56.3)**
n1α	140 (19.2)	313 (21.6)
n1β	52 (7.1)	134 (9.2)
n2	43 (5.9)	132 (9.1)**
n3	5 (0.7)	24 (1.7)
n4	0 (0.0)	6 (0.4)
Not operated	15 (2.1)	12 (0.8)*
Unknown	13 (1.8)	12 (0.8)*

* $P<0.05$, ** $P<0.01$.

Table III. Subjective Symptoms of the Breast Cancer Patients Detected by Mass Screening and in Out-patient Clinics

Subjective symptom	No. of subjects (%)	
	Mass screening	Out-patient clinics
−	235 (32.3)	18 (1.2)**
+	484 (66.5)	1,424 (98.2)**
Unknown	9 (1.2)	8 (0.6)
Total	728 (100.0)	1,450 (100.0)

** $P<0.01$.

Table IV. Mode of Discovery of the Tumor of Patients (with Subjective Symptoms) Detected by Mass Screening and in Out-patient Clinics

Opportunity of discovery	No. of subjects (%)	
	Mass screening	Out-patient clinics
Self-examination	130 (26.9)	225 (15.8)**
Fortuitous discovery	281 (58.1)	1,046 (73.5)**
Unknown	73 (15.1)	153 (10.7)*
Total	484 (100.0)	1,424 (100.0)

* $P<0.05$, ** $P<0.01$.

Table V. Histology of the Breast Cancers Detected by Mass Screening and in Out-patient Clinics

Histology	No. of subjects (%)	
	Mass screening	Out-patient clinics
Papillotubular ca.	190 (26.1)	375 (25.9)
Solid-tubular ca.	193 (26.5)	446 (30.8)*
Scirrhous ca.	215 (29.5)	442 (30.5)
Lobular ca.	15 (2.1)	24 (1.7)
Others	108 (14.8)	143 (9.9)**
Unknown	7 (1.0)	20 (1.4)
Total	728 (100.0)	1,450 (100.0)

* $P<0.05$, ** $P<0.01$.

the patients detected by mass screening. The T classification showed that Tis, T0 plus T1 were found in 38.7% of the patients detected by mass screening, and 29.7% of those found in the out-patient clinics, while T4 was found in 3.6% and 7.7%, again indicating that the size of tumors was significantly smaller in the patients detected by mass screening. Macroscopic and histological evidence of metastases in the regional lymph nodes similarly showed that early stages were more common in the patients detected by mass screening.

Subjective symptoms (mainly a lump or lumps, pain and nipple discharge, etc.) were absent in 32.3% of the patients detected by mass screening, and only 1.2% of those found in the out-patient clinics, while symptomatic patients were 66.5% and 98.2% respectively, indicating that subjective symptoms were significantly less common in the patients detected by mass screening (Table III).

Fortuitous discovery of tumor masses was common in all patients. However, discovery by breast self-examinations (BSE) was more common in the patients detected by mass screening with levels of 26.9% for mass screening and 15.8% for the out-patient clinics (Table IV).

The histology of breast cancer was compared between those detected by mass screening and those in the out-patient clinics (Table V). Solid-tubular carcinoma was more common in the patients detected in the out-patient clinics, and the incidence was 30.8% for these patients,

and 26.5% for those detected by mass screening. Carcinoma other than papillotubular carcinoma, solid-tubular carcinoma, scirrhous carcinoma, and lobular carcinoma was significantly more common in the patients detected by mass screening.

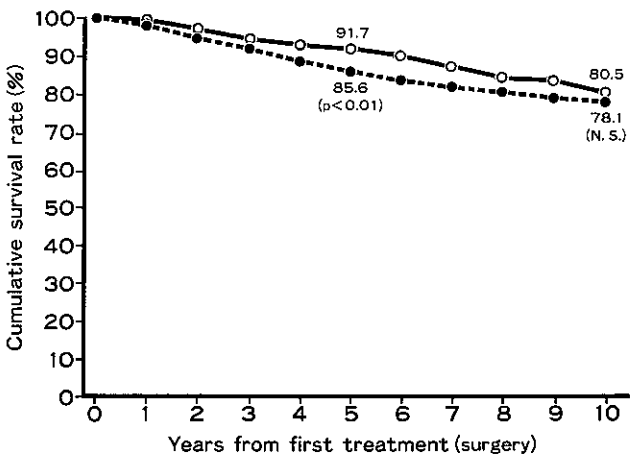

Fig. 1. Cumulative survival rate of patients with breast cancer detected by mass screening and in out-patient clinics. ○, patients detected by mass screening (n=720); ●, patients detected in out-patient clinics (n=1,440).

Prognosis Figure 1 shows the survival rate calculated by life table analysis separately for breast cancer detected by mass screening and that detected in the out-patient clinics. The 5-year survival rate was 91.7% for the patients detected by mass screening (n=720), and 85.6% for those found in the out-patient clinics (n=1,442). So, the survival rate was higher by 6.1% for the former patients, and this difference was statistically significant ($P<0.01$). The 10-year survival rates were 80.5% and 78.1%, respectively. The difference between the two groups had decreased to 2.4%, which was not statistically significant.

Survival of the patients detected by mass screening and those found in the out-patient clinics was analyzed in relation to clinical stage of the disease. The two groups did not differ greatly in this respect (Table VI). The survival rate was significantly higher at stage II, T2, and N0 in the patients detected by mass screening than those found in the out-patient clinics.

The cumulative survival rate was calculated from the time of the first treatment (surgery), although these results are not shown in the table. After 1975, the rate of 5-year survival was significantly higher in patients detected in mass screening. In contrast, before 1974, the survival rate was rather higher in patients detected in the out-patient clinics, whether for 5 or 10 years.

Some patients who were found to have breast cancer in the out-patient clinics, had undergone mass screening.

Table VI. Survival Rate of Patients Detected by Mass Screening and in Out-patient Clinics

	5-year survival (%)		10-year survival (%)	
	Mass screening	Out-patient clinics	Mass screening	Out-patient clinics
Stage grouping				
Tis	100.0	100.0	(100.0)	(100.0)
I	94.6	95.1	86.9	91.7
II	93.9	87.3**	85.1	80.5
III	67.9	62.6	40.7	45.1
Total	91.7	85.6**	80.5	78.0
T-primary tumor				
Tis, T0	100.0	100.0	(100.0)	(100.0)
T1	92.6	94.7	83.7	91.5
T2	93.6	86.4**	85.7	79.3
T3+T4	69.8	63.2	36.3	45.0
Total	91.4	85.5**	80.2	77.9
N-regional lymph nodes				
N0	95.9	92.0*	92.3	88.9
N1	90.1	86.2	71.4	76.2
N2+N3	58.8	37.5	(58.8)	(17.8)*
Total	91.4	85.5**	80.2	77.9

Figures within brackets ( ) in the table refer to an initial number of patients of 5 or less.
* $P<0.05$, ** $P<0.01$.

Table VII. Cumulative Survival Rate of Patients with Breast Cancer Detected by Mass Screening and in Out-patient Clinics

Opportunity of discovery	5-year survival (%)		10-year survival (%)	
	Mass screening	Out-patient clinics	Mass screening	Out-patient clinics
Self-examination	96.6	93.1	79.1	84.5
Fortuitous discovery	88.2	85.0	74.5	77.4
	90.5	86.1*	75.8	78.4

* $P<0.05$.

The survival rate was analyzed in relation to the history of mass screening. The 10-year survival rates tended to be higher in patients who had undergone mass screening.

Since some patients detected by mass screening had felt a lump in the breast or had had some symptoms before the mass screening, the survival rate was compared between symptomatic and asymptomatic patients. The 10-year survival rates indicated that the survival rate tended to be higher in the asymptomatic patients. The survival rate of symptomatic patients detected by mass screening was similar to that of patients found in the out-patient clinics, suggesting that the prognosis for symptomatic patients tended to be worse than that for asymptomatic patients.

The survival rate was also calculated according to reasons for detection. It tended to be higher with discovery by self-examination than discovery by chance, whether the cancer was detected by mass screening or in the out-patient clinics (Table VII).

DISCUSSION

Mass screening for breast cancer has spread rapidly and is now almost nationwide. This reflects the increased interest of adult women and the medical profession in breast cancer consequent upon the increased prevalence of the disease.

In the present study we compared clinical stage and prognosis of breast cancer detected by mass screening with that of breast cancer found in out-patient clinics as part of the effort to evaluate the life-prolonging effect of mass screening for breast cancer. The data on patients detected by mass screening were compared retrospectively with those on matched patients who had been found to have breast cancer in out-patient clinics. Many of the participating hospitals had conducted mass screening for breast cancer, and their data seemed to be reliable.

Breast cancer detected by mass screening is often at an early stage, and so the prognosis is good. The Health Insurance Plan (HIP) study reported that early detection was considered an important factor in reducing the mortality from breast cancer.[3-7] The study of the Breast Cancer Detection Demonstration Project (BCDDP)[8] and randomized control trials in Sweden[9,10] suggested that mass screening with mammography might lead to reduced mortality from breast cancer. In Japan, mass screening without mammography was carried out, and showed good results.[11,12] The present study also supports this general notion, and many patients detected by mass screening had early stage breast cancer (Table II).

Many patients detected by mass screening were free from subjective symptoms, suggesting that their tumors were small. Detection of breast cancer at such an early stage may be a key factor in improving the prognosis (Table III).

It is generally believed that the prognosis of solid-tubular carcinoma and scirrhous carcinoma is relatively poor. In the present study, the number of patients with solid-tubular carcinoma was significantly smaller in the patients detected by mass screening, and this might contribute to the better prognosis for these patients (Table V).

The overall survival curve for the patients detected by mass screening was compared with that for those found in the out-patient clinics. The data are very interesting (Fig. 1). The 5-year survival rate was clearly higher in the patients detected by mass screening, while the 10-year survival rate was only slightly higher in the same group of patients, and the difference from the other group was not significant. The question as to whether or not these results suggest that mass screening for breast cancer is of no value should be examined in further studies.

One of the likely reasons for the lack of a significant difference in the rate of 10-year survival between the two groups is that the survival rate was rather higher in the patients detected in the out-patient clinics if an early

series of patients (patients who were selected for the study before 1974) who had survived for more than 10 years at the time of the study were compared. Before 1974, mass screening might have picked up patients with breast cancer at more advanced stages than those of breast cancer detected in the out-patient clinics. After 1975, survival of the patients detected by mass screening exceeded the levels of the patients detected in the out-patient clinics, suggesting that the survival rate might improve in the patients detected by mass screening as the number of patients who have survived for more than 10 years increases.

Table VI shows the survival rate in relation to the degree of progression; it did not differ markedly, whether breast cancer was detected in mass screening or in the out-patient clinics. However, it was significantly higher at stage II, T2 and N0 in the patients detected in mass screening. This might be because breast cancer had progressed further in the patients detected in the out-patient clinics than in those found in mass screening even at the same stage of the disease. Other possible explanations are that breast cancer detected by mass screening might progress more slowly than that found in the out-patient clinics because of length bias, and mass screening could detect breast cancer earlier than out-patient clinics because of lead time bias. This might contribute to the higher survival rate in the patients detected by mass screening.[13] A fourth possibility is that there might be self-selection bias. Patients who underwent mass screening might pay more attention to relapse, and they might be more concerned with their health. As a result, survival of the patients detected in mass screening might be better. All these factors should be considered in assessing the effect of the mass screening.

Prognosis was better even in the patients detected in the out-patient clinics if they had undergone mass screening. One measure which we can take to improve the performance of mass screening is to educate the public so that they become more likely to participate in mass screening programs. Prognosis may be worse for symptomatic patients, such as those who feel a lump in the breasts, than for asymptomatic patients. Mass screening seems to be valuable if it can find asymptomatic patients who are still at a very early stage.

Lastly, the possible benefits of BSE have not yet been properly evaluated. The usual breast symptoms of the patients discovered by BSE are present to some degree in all women. However some authors[12, 14] reported evidence of the benefit of regular BSE, and the results of the present study strongly suggest the benefit of BSE. Discovery of breast cancer by BSE was more common in the patients detected by mass screening than in those detected in the out-patient clinics (Table IV). Table VII shows a tendency for better survival in patients who found masses by themselves.

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