

## A Case Control Study on the Effectiveness of Breast Cancer Screening by Clinical Breast Examination in Japan

Seiki Kanemura,<sup>1,2</sup> Ichiro Tsuji,<sup>1</sup> Noriaki Ohuchi,<sup>2,6</sup> Hiroyuki Takei,<sup>3</sup> Takao Yokoe,<sup>4</sup> Yukio Koibuchi,<sup>3</sup> Koji Ohnuki,<sup>2</sup> Akira Fukao,<sup>5</sup> Susumu Satomi<sup>2</sup> and Shigeru Hisamichi<sup>1</sup>

<sup>1</sup>Division of Public Health, Department of Social Medicine, Graduate School of Medicine, Tohoku University, 2-1 Seiryomachi, Aoba-ku, Sendai 980-8575, <sup>2</sup>Second Department of Surgery, Tohoku University School of Medicine, 1-1 Seiryomachi, Aoba-ku, Sendai 980-8574, <sup>3</sup>Second Department of Surgery, <sup>4</sup>Department of Emergency and Critical Care Medicine, Gunma University School of Medicine, 3-39-15 Showa-machi, Maebashi 371-8511 and <sup>5</sup>Department of Public Health, Yamagata University School of Medicine, 2-2-2 Iida-Nishi, Yamagata 990-9585

A case-control study was conducted in Miyagi and Gunma prefectures, Japan, to evaluate the effectiveness of breast cancer screening by clinical breast examination (CBE) alone in reducing breast cancer mortality. Case subjects, who were female and had died of breast cancer, were collected from residential registry files and medical records. Control subjects matched in sex, age and residence were randomly selected from residential registry files. The screening histories during 5 years prior to the cases having been diagnosed as breast cancer were surveyed using the examinee files of the screening facilities. Finally, the data of 93 cases and 375 controls were analyzed. The odds ratio (OR) of breast cancer death for participating in screening at least once during 5 years was 0.93 (95% confidence interval (95%CI) 0.48–1.79). The cases were more symptomatic than the controls when screened. If the participants who had had symptoms in their breasts were classified as not screened, the OR decreased to 0.56 (95%CI 0.27–1.18). The case control study suggests that the current screening modality (CBE) lacks effectiveness (OR=0.93), although it might be effective for an asymptomatic population (OR=0.56). The number of cases was small, and a larger case-control study is desirable to define whether CBE is effective or not. However, it is necessary to consider the introduction of mammographic screening to reduce breast cancer mortality in Japan.

Key words: Breast cancer — Effectiveness — Screening — Case control study

In Japan, 7,900 women died of breast cancer in 1996 and breast cancer was the fifth most common cause of death from cancer in females.<sup>1)</sup> Both mortality and incidence of breast cancer in Japan have been increasing, and are expected to keep increasing. Mass screening for breast cancer has been conducted for women aged 30 years and older all over Japan since 1987 under the Health and Medical Services Law for the Aged. The screening modality in this system is inspection and palpation of breasts and regional lymph nodes (clinical breast examination; CBE). In 1996, 3,187,084 females participated in the breast cancer screening; 134,244 females (4.2%) were recommended to go to hospitals for further diagnostic tests and 2,921 females (0.09%) were detected as having breast cancer.<sup>2)</sup>

Breast cancer screening by CBE was introduced into public health services in 1987 without any evidence concerning its effectiveness. It was based on the presumption that any early detection is always beneficial. Screening by CBE is rather expensive, because it is conducted by medical doctors. According to the 1995 survey by the Interna-

tional Breast Cancer Screening Network (IBSN), all of 22 countries except Japan have introduced mammography examination in their screening programs.<sup>3)</sup> In 1998 the Research Group for Evaluating the Effectiveness of Cancer Screening Programs in Japan (Chairperson: Dr. Shigeru Hisamichi) reported that the effectiveness of breast cancer screening by CBE has not yet been proven epidemiologically.

Most of the randomized controlled trials (RCTs),<sup>4–11)</sup> case-control studies<sup>12–18)</sup> and meta-analyses<sup>19, 20)</sup> in Western countries agree that, for subjects aged 50–69 years, screening mammography is significantly effective in reducing breast cancer mortality. These findings, however, would not apply to Japan because of the difference in screening modalities. It is urgently necessary to evaluate the effectiveness of screening for breast cancer by CBE in Japan. There has been one such study, which compared the survival rate between breast cancer patients detected at screening and those diagnosed at outpatient clinics.<sup>21)</sup> Five-year survival rate was significantly higher among those detected at screening (91.7% vs. 85.6%;  $P < 0.01$ ), but the statistical significance disappeared at 10 years (survival rate 80.5% vs. 78.1%; NS). Since comparison of sur-

<sup>6</sup>To whom correspondence should be addressed.

E-mail: noriakio@mail.cc.tohoku.ac.jp

vival rates is not free from lead-time bias, length bias, and so forth, further evidence is needed from a case-control study or intervention study. The objective of our study was to examine the effectiveness of breast cancer screening by CBE alone in reducing breast cancer mortality by means of case-control study. The present study consisted of relatively small sample size, but to our knowledge, it is the first such study in Japan.

**MATERIALS AND METHODS**

**Study setting** We selected Miyagi and Gunma prefectures, Japan, as study areas. In rural areas of Miyagi prefecture, screening for breast cancer has been carried out exclusively by the Miyagi Prefectural Cancer Society. In most municipalities of Gunma prefecture, breast cancer screening has been carried out by the Gunma Health Foundation. In both prefectures, screening for breast cancer using CBE alone was performed in accordance with the standards of the Health and Medical Services Law for the Aged. The records of the examinees, i.e., name, date of birth, address and results of screening test, were stored in these facilities.

The Miyagi Cancer Registry, a regional cancer registry covering all areas in this prefecture, also retains complete records, and the date of diagnosis of breast cancer for most cases can be ascertained from these records.

**Source population** We chose female residents in 54 municipalities in Miyagi and 55 in Gunma prefecture as the source population in this study. In these municipalities, the above two facilities have been exclusively conducting CBE screening for breast cancer.

**Identification of cases** Case subjects were defined as all the persons in the study area who had died of breast cancer from January 1993 to December 1995. In Miyagi prefecture, 54 municipalities were requested to select cases and compile lists giving the name, date of birth, date of death and address of each case, using the residential registry files. In Gunma prefecture, 48 major hospitals were requested to select cases and compile lists, using the medical records. Forty-seven municipalities (87%) responded in Miyagi prefecture and 48 hospitals (100%) in Gunma prefecture. A total of 159 cases were collected, 111 cases from Miyagi prefecture and 48 cases from Gunma prefecture. In Gunma prefecture, there were 311 breast cancer deaths from January 1993 to December 1995. Our cases corresponded to 15.4% of the decedents at Gunma prefecture. There was no significant difference, however, in age distribution between the present cases at Gunma and the decedents who were not included in the present study. For all these potential cases, the dates of diagnosis of breast cancer were identified and the causes of death were ascertained using the medical records of major hospitals and the records of the Miyagi Cancer Registry.

Seven patients who had been living in other prefectures before diagnosis were excluded (Table I). Twenty-two patients who had died before 34 years of age were excluded, since their chances of participation in screening would be limited; screening under the Law was offered to women aged 30 years and over, and some patients who had died before age 34 would have been diagnosed at younger than 30 years. Another 2 cases were excluded because their date of diagnosis could not be confirmed. We excluded another 10 cases because they had been diagnosed as breast cancer before the screening program started. As a result, a total of 118 cases remained for our study.

**Identification of controls** We requested municipalities to randomly select 4 or 5 (4 in Miyagi prefecture and 5 in Gunma prefecture) control subjects, matched in year of birth (within 2 years), sex and address (administrative district), for each case from residents who were living at the time when the case died, using the residential registry files. For the 118 cases, a total of 521 controls were selected.

**Identification of screening histories** For the 118 cases and their controls, screening histories during 5 years prior to each diagnosis of breast cancer were surveyed using examinee files of the Miyagi Cancer Society and the Gunma Health Foundation. Examinee files were stored in the form of printed documents, and the files since 1974 were available at the Miyagi Cancer Society and those since 1988 at the Gunma Health Foundation. The first and last names, date of birth, and address were used for identifying the screening histories.

Twenty-three cases and their controls were excluded because information on the screening histories of cases was not available. Because 2 cases had no controls after the data treatment mentioned above, they were excluded. Finally, 93 cases and 375 controls were eligible for the present study. Eighteen sets (18 cases and 90 controls) were matched in the proportion of 1 to 5 and 67 sets were matched in the proportion of 1 to 4. Three sets each were matched in the proportions of 1 to 3 and 1 to 2 and 2 sets were matched in the proportion of 1 to 1.

Table I. Cases Excluded from or Included in the Study

No. of initial cases	159
No. of cases excluded	66
Lived in other prefectures at the time of diagnosis	7
Died before 30 years of age	22
Date of diagnosis unconfirmed	2
Diagnosed before the start of screening	10
Screening history unconfirmed	23
Without controls	2
No. of cases included	93

If one-third of the cases had participated in screening, approximately 74 matched pairs (4 controls for one case) would be required to significantly detect the relative risk of 0.5 (significance 5%, power 80%).<sup>22)</sup> Consequently, we considered that we could determine whether screening reduced the mortality for breast cancer by half, which is comparable with the reported odds ratios (ORs) of breast cancer screening in Western countries.

**Data analysis** Conditional logistic-regression models for the matched sets were used to estimate ORs and their 95% confidence intervals (95% CIs).<sup>23)</sup> The crude ORs were calculated for those participating in the screening at least once during the index interval before the case diagnosis, as compared with no participation in screening during this period. To evaluate the effectiveness between age groups, we calculated ORs in two subgroups (diagnosed at aged 35–49 years and aged over 50). Analyses were carried out with PHREG in the SAS computer program.<sup>24)</sup> We adopted  $P < 0.05$  as the criterion of statistical significance.

**Screening modality: clinical breast examination** The conventional first stage screening consisted of CBE, e.g., inspection and palpation, of the breasts and the regional lymph nodes. The subjects with any abnormal findings detected by the CBE entered the second stage of screening

with mammography and ultrasonography. Women who required aspiration biopsy cytology or surgical biopsy were referred to community hospitals. The participating doctors had clinical experience in general surgery for more than 5 years.

## RESULTS

The age distributions of cases and controls by age at the diagnosis of the cases are shown in Table II. The forties and fifties were most frequent. In cases, the mean age at diagnosis was 52.8 years (range: 35–86). Thirty-five cases (38%) were diagnosed before 1990, and 58 cases (62%) in 1990 or later. The mean interval between the date of diagnosis and the date of death was 4.1 years (range: 0–15).

The participation rate in breast cancer screening among the cases and controls is shown in Table III. It was 17% in cases and 18% in controls within one year before the diagnosis of the cases, and 24% in cases and 25% in controls within two years. There were no significant differences in the participation rates between cases and controls at either interval.

Table II. Distribution of Cases and Controls by Age at the Diagnosis of Cases; Miyagi and Gunma, Japan, 1993–1995

Age	Cases (%)	Controls (%)
35–39	8 (9)	36 (10)
40–49	34 (36)	124 (33)
50–59	29 (31)	111 (29)
60–69	11 (12)	55 (15)
70–	11 (12)	49 (13)
Total	93 (100)	375 (100)

Table IV. Odds Ratio of Participating in Screening for Breast Cancer Death (Aged 35–49 and over 50)

Interval <sup>a)</sup> (year)	Aged 35–49		Aged over 50	
	OR <sup>b)</sup>	(95% CI <sup>c)</sup> )	OR <sup>b)</sup>	(95% CI <sup>c)</sup> )
1	1.10	(0.37–3.23)	0.76	(0.32–1.80)
2	0.89	(0.30–2.66)	0.75	(0.34–1.66)
3	0.70	(0.24–2.03)	0.53	(0.23–1.20)
4	0.56	(0.20–1.58)	0.51	(0.22–1.16)
5	0.46	(0.15–1.40)	0.59	(0.24–1.40)

a) Interval, years before diagnosis of the cases.

b) OR, odds ratio.

c) CI, confidence interval.

Table III. Odds Ratio of Breast Cancer Death for the Subjects Participating in Screening at Least Once during the Index Interval

Interval <sup>a)</sup> (year)	Cases		Controls		OR <sup>c)</sup>	(95% CI <sup>d)</sup> )
	Number	% participated <sup>b)</sup>	Number	% participated <sup>b)</sup>		
1	93	17	375	18	0.93	(0.48–1.79)
2	88	24	347	25	0.86	(0.46–1.60)
3	83	24	328	31	0.63	(0.33–1.18)
4	80	25	319	33	0.57	(0.30–1.07)
5	75	25	299	33	0.59	(0.31–1.14)

a) Interval, years before diagnosis of the cases.

b) % participated, percentage of those who had ever participated in screening within each interval.

c) OR, odds ratio.

d) CI, confidence interval.

Table V. Rate of Symptomatic Participants in Screening

Years before diagnosis	Cases		Controls		P value <sup>b)</sup>
	Available	% symptomatic <sup>a)</sup>	Available	% symptomatic <sup>a)</sup>	
1	12	42	37	0	0.0004
2-5	17	18	73	4	0.079

a) % symptomatic, percentage of those who had symptoms in their breasts at the time of screening.

b) P value was tested by Fischer's exact test.

Table VI. Odds Ratio of Breast Cancer Death for the Subjects Participating in Screening at Least Once during the Index Interval When the Symptomatic Participants Are Classified as Those Who Were Not Screened

Interval <sup>a)</sup> (year)	OR <sup>b)</sup>	(95%CI <sup>c)</sup>
1	0.56	(0.27-1.18)
2	0.60	(0.30-1.17)
3	0.48	(0.25-0.93)
4	0.44	(0.23-0.84)
5	0.45	(0.22-0.89)

a) Interval, years before diagnosis of the cases.

b) OR, odds ratio.

c) CI, confidence interval.

The OR of breast cancer death for participating in screening is also shown in Table III. The OR was 0.93 (95%CI 0.48-1.79) within one year, and 0.86 within two years, gradually decreasing to 0.59 within five years. But none was statistically significant.

The result of further analysis by subgroups, aged 35-49 years and over 50 respectively, is shown in Table IV. For those aged 35-49 years, the OR was 1.10 (95%CI 0.37-3.23) within one year, while for those aged over 50 years, the OR was 0.76 (95%CI 0.32-1.80) within one year. The OR gradually decreased with longer index interval for both those aged 35-49 and those over 50, but the changes were not statistically significant.

Among the participants in breast cancer screening, the frequency of those admitting breast symptoms was compared between cases and controls (Table V). In the screening within one year before diagnosis, 42% of the cases were symptomatic, versus none in the controls. The rate of symptomatic participants among the cases decreased to 18% in the screenings within 2-5 years before diagnosis. Thus, cases with subjective symptoms were more likely to newly participate in the screening at which they were detected as having breast cancer. Weiss reported that there is a possibility of underestimating the effectiveness of the screening, when those who participated in the screening because they felt some symptoms are classified as those who were "screened" in the data analysis.<sup>25)</sup> Then, as a

sub-analysis, we classified the symptomatic participants as those who were not screened and calculated the ORs according to the proposal by Weiss. The ORs of breast cancer death, when the participants who had symptoms in their breasts were classified as those who were not screened, are shown in Table VI. The OR was 0.56 (95%CI 0.27-1.18) within one year. Although not statistically significant, the results may suggest the effectiveness of screening by CBE for an asymptomatic population.

## DISCUSSION

When cancer screening is conducted as public policy, its effectiveness has to be proved. This is the first population-based case-control study to evaluate breast cancer screening in Japan. We collected cases from municipalities and hospitals, and the response rate was high (87% in Miyagi prefecture and 100% in Gunma). Although only 93 out of the original 159 cases were eligible for analysis, there was no difference in age distribution between the eligible cases (N=93) and the excluded cases (N=66) (data not shown). The controls were randomly selected from residential registry files. The participation rate in controls was similar in each prefecture. Accordingly, there seems to be little selection bias in our data, and the present controls were representative of the study area. Since the screening histories for the cases and controls were based on the same data source, recall bias was eliminated.

In our data, the OR of breast cancer death for participating in screening was 0.93 within one year (Table III) and effectiveness of breast cancer screening by CBE alone was not proved. Before interpreting the present results, however, we should point out there are limitations in this study. First, the present study consisted of relatively small sample size. In order to detect the OR of 0.93 significantly, we would have to collect more than 8,000 cases. Thus, the present study lacked the statistical power to detect such a small effect. However, as compared to the ORs of other cancer screenings in Japan (0.4 in gastric cancer,<sup>26)</sup> 0.4 in colorectal cancer<sup>27)</sup> and 0.2 in cervical cancer<sup>28)</sup>, the OR of 0.93 for breast cancer screening is much closer to 1.0, suggesting a null effect. Second, self-selection bias was not controlled in this study, because

such information as life style associated with breast cancer risk was not available. If participants in screening had lower risk than non-participants, the effectiveness of a screening would be overestimated by the present study. However, since the OR in our study was near 1.0 and was not statistically significant, it is not likely that the self-selection bias affected our conclusion, that is, lack of effectiveness.

As shown in Table V, the rate of symptomatic participants in screening was higher within 1 year before diagnosis than within 2–5 years. Five out of the 12 symptomatic cases participated in the screening for the first time within year of diagnosis. Therefore, it is suggested that a certain fraction of the cases participated in the screenings because they recognized some symptoms in their breasts. There seemed to be two different groups among the participants; those who regularly participated in screening without any symptom (healthy screenees and self-selection), and those who newly participated because they felt some symptoms, and the latter participated closer to the diagnosis of breast cancer. As the fraction of the participants of the former group increases, the efficacy of cancer screening under the case-control study design may be overestimated because of healthy screenee bias<sup>29)</sup> and self-selection bias. Therefore, the lower OR with extended index intervals (Table III) could be interpreted as the effect of the above two biases. To reduce the influence of symptomatic patients, we classified these participants as those who were not screened and calculated the ORs again. As a result, the OR declined from 0.93 to 0.56 (Table IV). These results suggest that the current screening modality might be effective for an asymptomatic population (OR=0.56), but that the current screening system lacks effectiveness (OR=0.93) because of the aggregation of symptomatic subjects among the participants.

The present results and the previous studies are in agreement in concluding that the current breast cancer screening in Japan by CBE alone appears to be ineffective. Ota *et al.* reported that there was no difference of 10-year survival rate between the breast cancer patients detected at screening and those diagnosed at outpatient clinics.<sup>21)</sup> According to the result of a national survey in Japan,<sup>30)</sup> the proportion of early-staged breast cancers was not different between the patients detected at screening and those diagnosed at outpatient clinics.

Two factors may be responsible for the lack of effectiveness of breast cancer screening in Japan. One is the

low sensitivity of CBE. Ohuchi *et al.* reported that for women aged over 50 the sensitivity of screening mammography (SMG) combined with CBE was 97.2%, while the sensitivity of CBE alone was 84.6%.<sup>31)</sup> The sensitivity of CBE alone was lower than that of SMG. Second, those who already had symptoms in their breasts tended to participate in screening, although this reflects the real state of breast cancer screening in Japan and is an intrinsic feature of this system.

The breast cancer screening by CBE in Japan failed to show effectiveness partly because of insufficient sensitivity of the test and partly because of symptomatic participants. In Western countries, SMG has already been proved to be effective in reducing breast cancer mortality at aged 50–69. In Japan, the effect of SMG on mortality reduction has not been evaluated. Even among the current participants, however, it was proved that SMG was superior to CBE in terms of detection rate, especially in detection of early-staged cancer.<sup>31,32)</sup> Ohuchi *et al.* reported that a higher rate (73%) of early-staged breast cancer (stage 0 and stage I in TNM Clinical Classification by UICC) was detected by SMG combined with CBE, as compared to that (39%) by CBE.<sup>31)</sup>

There are some limitations in this study. First, as already discussed, the small sample size prevented us from reaching a definite conclusion. Second, there is some possibility that the cases and controls had received screening in addition to that by the Miyagi Prefectural Cancer Society and the Gunma Health Foundation. This misclassification might interfere with the present estimate of OR.

It is desirable to conduct another case-control study on the effectiveness of CBE in another area of Japan to confirm our results. However, we should urgently consider nation-wide introduction of mammography for breast cancer screening to reduce breast cancer mortality in Japan.

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