Jpn. J. Cancer Res. 82, 27–32, January 1991

The Effect of Mass Screening for Breast Cancer: Results of a Multivariate Analysis

Tetsuo Kuroishi,[1] Suketami Tominaga,[2] Jun Ota,[3] Toshio Horino,[3] Tetsuo Taguchi,[3] Tsunehiro Ishida,[4] Takao Yokoe,[4] Masaru Izuo,[4] Masami Ogita,[5] Sueyoshi Itoh,[6] Rikiya Abe,[7] Koichi Yoshida,[8] Tadaoki Morimoto,[9] Kohji Enomoto,[10] Hideya Tashiro,[11] Yoshitomo Kashiki,[12] Satoru Yamamoto,[12] Choichiro Kido,[13] Kazuyoshi Honda,[14] Michizou Sasakawa,[14] Mamoru Fukuda[15] and Hiromu Watanabe[15]

[1]Division of Epidemiology, [2]Aichi Cancer Center Research Institute, 1-1 Kanokoden, Chikusa-ku, Nagoya 464, [3]Department of Oncologic Surgery, The Research Institute for Microbial Disease, Osaka University, 3-1 Yamadagaoka, Suita 565, [4]Second Department of Surgery, Gunma University School of Medicine, 3-39-15 Showa-cho, Maebashi 371, [5]Department of Surgery, National Sapporo Hospital, 4-2-3-54 Kikusui, Shiraishi-ku, Sapporo 003, [6]Itoh Surgery Clinic, 12-13 Fudaba, Kochi 780, [7]Second Department of Surgery, Fukushima Prefectural College, 1 Hikarigaoka, Fukushima 960-12, [8]Department of Surgery, Miyagi Seijinbyo Center, Shiote, Medeshima, Natori 981-12, [9]Second Department of Surgery, School of Medicine, The University of Tokushima, 3-18-15 Kuramoto-cho, Tokushima 770, [10]Department of Surgery, Keio University School of Medicine, 35 Shinano-machi, Shinjuku-ku, Tokyo 160, [11]Department of Breast Surgery, National Kyusyu Cancer Center Hospital, 595 Notame, Minami-ku, Fukuoka 815, [12]Department of Surgery, Gifu Koseiren Gihoku Hospital, 1187-3 Takatomi-cho, Yamagata-gun, Gifu 501-21, [13]Department of Diagnostic Radiology, Aichi Cancer Center Hospital, 1-1 Kanokoden, Chikusa-ku, Nagoya 464, [14]Department of Diagnostic Imaging, Surgery, Tochigi Cancer Center, Younan, Utsunomiya 320 and [15]First Department of Surgery, St. Marianna University School of Medicine, 2-16-1 Sugou, Miyamae-ku, Kawasaki 213

To evaluate the life-prolonging effect of mass screening for breast cancer, we compared the risk of death for the patients detected by mass screening with that for the patients diagnosed in out-patient clinics, after adjusting for other relevant factors simultaneously by using the Cox regression model. A multivariate analysis using the Cox regression model in which clinical staging of disease was taken as one of the independent variables, showed that the risk of death for patients detected by mass screening was smaller by 0.765 times than that for patients found in out-patient clinics although the reduction was not statistically significant. This small reduction might be partly due to the effect of mass screening through early detection even within the same stage, and partly due to length bias, lead time bias and self-selection bias. When clinical staging of disease was removed from the independent variables, the risk of death for patients detected by mass screening was reduced from 0.765 times to 0.677 times that for patients diagnosed in out-patient clinics, which was statistically significant ($P<0.01$). For asymptomatic patients detected by mass screening, such a reduction of the risk of death was from 0.789 times to 0.555 times that for patients found in out-patient clinics ($P<0.05$). These results suggest that mass screening for breast cancer may contribute to the reduction of the risk of death, although the effect of biases inherent in periodic screening was not removed completely in the present analysis.

Key words: Breast cancer screening — Matched pair analysis — Multivariate analysis — Prognosis — Life-prolonging effect

Mass screening for breast cancer has spread rapidly in recent years, and is today almost nationwide in Japan.[1-3] Physical examination by a physician has been adopted as a standard detection modality for breast mass screening in almost all areas of Japan.[1-3] It is considered necessary to evaluate the life-prolonging effect of breast cancer screening programs.

In the previous paper,[4] to investigate the life-prolonging effect of breast cancer screening, we compared the clinical stage and prognosis of breast cancer patients detected by mass screening with those for matched patients found in out-patient clinics. The stage Tis or I was found in 40.9% of the patients detected by mass screening, and in 28.7% of those found in out-patient clinics, indicating that early stages were significantly more common in the patients detected by mass screening. The 5-year survival rate was significantly higher in the patients detected by mass screening that in those in out-patient clinics ($P<0.01$), while the 10-year survival rate was only slightly higher (the difference was not significant).

As partly shown in the previous paper, factors related to the survival were correlated with each other, such as clinical stage of disease, method of detection, year of

treatment, age at initial treatment, history of screening and so on. The purpose of the present study was to evaluate the life-prolonging effect of mass screening for breast cancer, after adjustment for potential confounding factors. For this purpose, we compared the risk of death for the patients detected by mass screening with that for the patients found in out-patient clinics, after adjusting for other relevant factors simultaneously by using the Cox regression model.[5]

SUBJECTS AND METHODS

The subjects of this study were the same as those described in the previous paper.[4] In brief, the Research Group on the Study of Mass Screening for Breast Cancer (chief researcher: S. Tominaga), organized in 1987 with the support of Grants-in-Aid from the Ministry of Health and Welfare of Japan, has conducted a collaborative study to assess the life-prolonging effect of mass screening for breast cancer. A total of 728 patients detected by mass screening and 1,450 patients found in out-patient clinics, matched for hospital, age and the time of treatment, were reviewed in 11 regions of Japan.

Univariate and multivariate analyses of factors related to the survival were performed by means of the Cox regression model to investigate the single and the joint effect of factors such as clinical stage, detection method, year of treatment, age at initial treatment and history of screening. Excluding the cases with missing data from the above patients, 720 patients detected by mass screening and 1,442 in the out-patient clinics were used in the present analysis. The values/scores of variables employed in the Cox regression model are shown in Table I.

Furthermore, to investigate the life-prolonging effect of breast mass screening under the ideal situation that all screenees have no symptoms, we compared the survival rates for asymptomatic patients (N=233) detected by mass screening and for patients (N=1,442) diagnosed in out-patient clinics. Cumulative survival rate was calculated by the actuarial method.[6] Testing to determine the significance of the difference between survival rates at a certain point of time was done based on standard errors of cumulative survival rates estimated by using Greenwood's formula. The logrank test of the difference between the survival curves over an observed period was employed.[7] Similar multivariate analyses using the Cox regression model mentioned above were also carried out in these cases.

RESULTS

Table II shows the results of univariate analysis of factors related to overall survival using the Cox regression model. Clinical stage, detection method and year of treatment had a significant effect on the survival, when singly tested.

The difference in the risk ratio of death for patients detected by mass screening compared to those found in out-patient clinics between when adjusting for stage of disease in a multivariate analysis and when not adjusting for stage is considered to be attributable to breast cancers detected by mass screening being at an earlier stage.

Table III shows the results of multivariate analysis employing the Cox regression model in which stage of

Table I. Values/Scores of Variables Used in the Cox Regression Model

Prognostic factor	Values/Scores
Clinical stage	0: Tis, 1: I, 2: II, 3: IIIa, IIIb, 4: IV
Detection method	0: Mass screening, 1: Out-patient clinics
Year of treatment	1: 1968–1979, 2: 1980–1987
Age at initial treatment	Age of each patient
History of screening	0: Never, 1: 3 yr & over, 2: within 2 yr

Table II. Univariate Analysis of Factors Related to Survival in the Cox Regression Model for Patients Detected by Mass Screening and in Out-patient Clinics (N=2,168)

Factor	Regression coefficient (B)	Standard error of B	*t* value	Statistical significance level (*P*)	Risk ratio (fav./unfav.)[a]
Clinical stage	1.161	0.083	14.05	<0.001	0.031 (Stage I/Stage IV)
Detection method	0.391	0.138	2.83	<0.01	0.677 (screening/out-patient clinics)
Year of treatment	−0.525	0.131	−4.00	<0.001	0.592 (1980–87/–1979)
Age at initial treatment	0.012	0.006	1.92	NS	0.702 (30 yr/60 yr)
History of screening	−0.150	0.135	−1.10	NS	0.742 (within 2 yr/never)

a) Risk ratio for favorable characteristic versus unfavorable one.

Table III. Multivariate Analysis of Factors Related to Survival in the Cox Regression Model for Patients Detected by Mass Screening and in Out-patient Clinics (N=2,168): When Clinical Stage is Included in the Independent Variables

Factor	Regression coefficient (B)	Standard error of B	*t* value	Statistical significance level (*P*)	Risk ratio (fav./unfav.)[a]
Clinical stage	1.159	0.084	13.87	<0.001	0.031 (Stage I/Stage IV)
Detection method	0.268	0.144	1.86	NS	0.765 (screening/out-patient clinics)
Year of treatment	−0.539	0.134	−4.03	<0.001	0.583 (1980–87/–1979)
Age at initial treatment	0.015	0.006	2.39	<0.05	0.636 (30 yr/60 yr)
History of screening	0.112	0.141	0.79	NS	0.800 (never/within 2 yr)

a) Risk ratio for favorable characteristic versus unfavorable one.

Table IV. Multivariate Analysis of Factors Related to Survival in the Cox Regression Model for Patients Detected by Mass Screening and in Out-patient Clinics (N=2,168): When Clinical Stage is Excluded from the Independent Variables

Factor	Regression coefficient (B)	Standard error of B	*t* value	Statistical significance level (*P*)	Risk ratio (fav./unfav.)[a]
Detection method	0.391	0.144	2.71	<0.01	0.677 (screening/out-patient clinics)
Year of treatment	−0.549	0.133	−4.14	<0.001	0.577 (1980–87/–1979)
Age at initial treatment	0.014	0.006	2.30	<0.05	0.653 (30 yr/60 yr)
History of screening	0.018	0.141	0.13	NS	0.964 (never/within 2 yr)

a) Risk ratio for favorable characteristic versus unfavorable one.

disease, detection method, year of treatment, age at initial treatment, and history of screening were treated as independent variables. Clinical stage, year of treatment, and age at initial treatment were significantly related to the survival. However, detection method did not have a significant effect on the survival. But the risk ratio of death was 0.765 for patients detected by mass screening compared to that for those diagnosed in out-patient clinics.

Table IV shows the results of a multivariate analysis in which stage of disease was removed from the independent variables. In this case, detection method was found to be significantly related to the survival ($P<0.01$) as well as year of treatment and age at initial treatment. The risk of death for patients detected by mass screening was 0.677 times that for patients found in out-patient clinics.

Results from the two multivariate analyses using the Cox regression model indicate that stage of disease and detection method exert a significant effect on the survival. However, while stage is related to the survival in a direct manner, detection method exerts an effect on the survival through its influence upon the stage of disease at the time of detection.

Mass screening is considered to be of great value to detect asymptomatic patients at a very early stage. To investigate the effectiveness of mass screening under such an ideal situation, we compared the survival for asymptomatic patients detected by mass screening with that for patients found in out-patient clinics. The 5-year survival was 93.6% for asymptomatic patients detected by mass screening (N=233), and was higher by 8.0% than that (85.6%) for patients found in out-patient clinics (N=

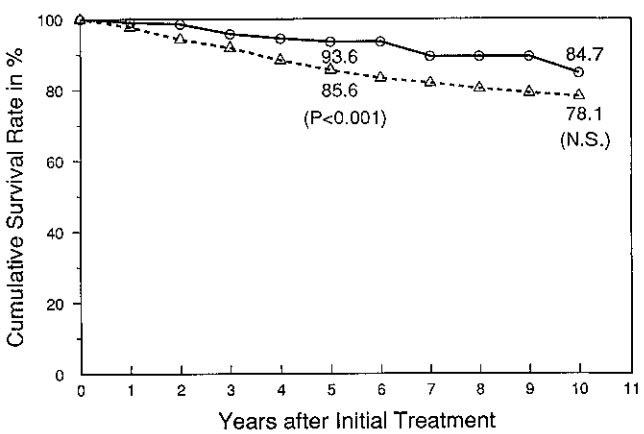

Fig. 1. Cumulative survival rates for 233 asymptomatic breast cancer patients detected by mass screening (○) and for 1,442 patients diagnosed in out-patient clinics (△).

Table V. Multivariate Analysis of Factors Related to Survival in the Cox Regression Model for Patients without Symptoms Detected by Mass Screening and for Patients Found in Out-patient Clinics (N=1,675): When Clinical Stage is Included in the Independent Variables

Factor	Regression coefficient (B)	Standard error of B	*t* value	Statistical significance level (*P*)	Risk ratio (fav./unfav.)[a]
Clinical stage	1.186	0.093	12.72	<0.001	0.029 (Stage I/Stage IV)
Detection method	0.237	0.265	0.90	NS	0.789 (screening/out-patient clinics)
Year of treatment	−0.499	0.147	−3.39	<0.001	0.607 (1980–87/–1979)
Age at initial treatment	0.020	0.007	2.78	<0.01	0.554 (30 yr/60 yr)
History of screening	−0.022	0.213	−0.10	NS	0.957 (within 2 yr/never)

a) Risk ratio for favorable characteristic versus unfavorable one.

Table VI. Multivariate Analysis of Factors Related to Survival in the Cox Regression Model for Patients without Symptoms Detected by Mass Screening and for Patients Found in Out-patient Clinics (N=1,675): When Clinical Stage is Excluded from the Independent Variables

Factor	Regression coefficient (B)	Standard error of B	*t* value	Statistical significance level (*P*)	Risk ratio (fav./unfav.)[a]
Detection method	0.589	0.264	2.23	<0.05	0.555 (screening/out-patient clinics)
Year of treatment	−0.512	0.147	−3.49	<0.001	0.599 (1980–87/–1979)
Age at initial treatment	0.018	0.007	2.66	<0.01	0.578 (30 yr/60 yr)
History of screening	−0.077	0.214	−0.36	NS	0.857 (within 2 yr/never)

a) Risk ratio for favorable characteristic versus unfavorable one.

1,442) (Fig. 1). This difference was statistically significant ($P<0.001$). The 10-year survival rate for asymptomatic patients was 84.7%, and higher by 6.6% than that (78.1%) for out-patient cases, but the difference was not statistically significant. The overall difference between the two curves was statistically significant by the logrank test ($P<0.01$).

For asymptomatic patients detected by mass screening, the risk of death was 0.789 times (statistically not significant) that for patients found in out-patient clinics when clinical stage was included in the independent variables (Table V), and was 0.555 times ($P<0.05$) when clinical stage was excluded from the independent variables (Table VI).

DISCUSSION

A randomized controlled trial such as that used in the HIP (Health Insurance Plan of Greater New York) study[8] or the Swedish study[9] for breast cancer screening has been considered as the most accurate method to evaluate the effectiveness of mass screening for breast cancer. These studies suggested that mass screening with mammography might lead to reduced mortality from breast cancer. However, mass screening programs carried out in most areas of Japan have consisted of questionnaire survey, inspection and palpation by a physician. No randomized trial for breast cancer screening has been conducted in Japan, because of difficulties in carrying out such experimental trials.

Alternative methods to a randomized trial are the case-control study approach to compare the history of mass screening, and comparisons of the mortality trends in similar populations with different coverage-rates of screening. In Japan, case-control studies were conducted for stomach cancer screening[10] and for uterine cancer screening.[11] Mortality trends studies were carried out for stomach cancer screening[12] and for uterine cancer screening.[13] Unfortunately, these approaches have not been conducted for breast cancer mass screening in Japan.

Morimoto *et al.*[14] reported that the 15-year survival rate of a group of breast mass screening cases in Tokushima Prefecture, Japan was slightly higher than that of a group of out-patient clinic cases, but the difference was not significant. Ishida *et al.*[15] obtained similar results in a comparison of the 8-year survival rates between mass screening cases and out-patient cases in Gunma Prefecture, Japan.

In our previous paper,[4] we investigated and compared clinical stage and prognosis of breast cancer patients detected by mass screening with those for matched patients found in out-patient clinics. Early stage breast cancers were significantly more common in the patients detected by mass screening. The 5-year survival rate was significantly higher in the patients detected by mass screening than in those in out-patient clinics ($P<0.01$), while the 10-year survival rate was slightly higher, but the difference was not significant.

Generally speaking, factors related to the survival were correlated with each other, such as stage of disease, method of detection, year of treatment, age at treatment, history of screening and so on. To make clear the effectiveness of mass screening for breast cancer, we compared the risk of death of the patients detected by mass screening with that of the patients in out-patient clinics, after adjusting for other relevant factors simultaneously by means of the Cox regression model.

A multivariate analysis in which clinical stage of disease was considered as one of the independent variables showed that clinical stage, year of treatment, and age at initial treatment were significantly related to the survival (Table III). Treatment methods might have been improved in recent years, and younger woman might carry out self-examination of their own breasts more frequently than aged women. Detection method did not have a significant influence on the survival, after adjusting for clinical stage as well as other relevant factors. However, the risk of death for patients detected by mass screening was 0.765 times that for patients in out-patient clinics. This might be partly due to early detection by mass screening even within the same stage, and partly due to length bias, lead time bias and self-selection bias.

Multivariate analysis using the Cox regression model in which stage of disease was removed from the independent variables indicated that detection method was significantly related to survival ($P<0.01$) (Table IV). The reduction of the risk ratio from 0.765 to 0.677 when stage of the disease was removed from among the factors was considered due to the effect of mass screening through early detection.

One plausible explanation of the fact that this reduction of the risk ratio was not so large is that the survival rate was fairly high even in the patients detected in out-patient clinics. Another is that a fairly large proportion (66.5%) of the patients detected by mass screening had already recognized a lump or lumps in their breasts as shown in the previous paper.[4] Mass screening seems to be of great value to detect asymptomatic cancers which are still at a very early stage. So, the overall survival curve for patients without symptoms detected by mass screening was compared with that for patients found in out-patient clinics (Fig. 1). The risk of death for asymptomatic patients detected by mass screening was reduced from 0.789 times to 0.555 times that for patients found in out-patient clinics when stage of the disease was removed from among the independent variables (Table V and Table VI). This fairly large reduction suggested that the life-prolonging effect might be improved if mass screening could detect only asymptomatic breast cancers at a very early stage.

There might be room for improvement of the effectiveness of mass screening for breast cancer. From a public education point of view, it should be emphasized that symptomatic patients who find lumps should visit an out-patient clinic/detection center as early as possible.

Modalities other than physical examination could be taken into consideration for initial mass screening to detect preclinical or nonpalpable cancer.[16] According to the reports of the Breast Cancer Detection Demonstration Project (BCDDP),[17] breast cancer is frequently detected by mammography alone or by mammography combined with physical examination. The 5-year survival rate was highest in patients detected by mammography alone. In recent years, mammography equipment has improved remarkably with respect to dosage of radiation, cost and computerization.[18, 19]

Even if mammography, or cytology of nipple discharge, etc., are introduced as an initial screening modality, alone or in combination with physical examination, it will be necessary to evaluate the effectiveness of mass screening with such a modality in respect of reduced mortality from breast cancer and cost-effect and cost-benefit relationships, before such a mass screening is implemented widely.

ACKNOWLEDGMENTS

The present study was supported in part by Grants-in-Aid for Cancer Research (No. 62-34, No. 1-13) from the Ministry of Health and Welfare of Japan. We are indebted to all the members of the Research Group on the Study of Mass Screening for Breast Cancer.

(Received July 17, 1990/Accepted October 8, 1990)

REFERENCES

1) Watanabe, H., Yamaguchi, S., Fukuda, M., Itoh, S., Ogita, M., Tashiro, H., Abe, R., Yoshida, K., Ishida, T., Izuo, M., Morimoto, T., Taguchi, T., Ota, J., Horino, T., Kido, C., Kashiki, Y., Sasakawa, M., Honda, K., Enomoto, K., Tominaga, S. and Kuroishi, T. An overview of breast cancer mass screening in Japan. *J. Jpn. Soc. Cancer Ther.*, **25**, 103–111 (1990) (in Japanese).
2) Proceedings of the 39th general meeting of the Japan Mammary Cancer Society, Report of a questionnaire (Kagoshima) 1984.
3) Kuroishi, T., Tominaga, S. and Nakahara, T. Current trends in mass screening for breast cancer by municipalities in Japan — a report of the National Survey on Breast Cancer Control by Municipalities in Japan in 1984. *Jpn. J. Breast Cancer*, **1**, 285–291 (1986) (in Japanese).
4) Ota, J., Horino, T., Taguchi, T., Ishida, T., Izuo, M., Ogita, M., Abe, R., Watanabe, H., Morimoto, T., Itoh, S., Tashiro, H., Yoshida, K., Honda, K., Sasakawa, M., Enomoto, K., Kashiki, Y., Kido, C., Kuroishi, T. and Tominaga, S. Mass screening for breast cancer: comparison of the clinical stages and prognosis of breast cancer detected by mass screening and in out-patient clinics. *Jpn. J. Cancer Res.*, **80**, 1028–1034 (1989).
5) Cox, D. R. Regression models and life-tables. *J. R. Stat. Soc.*, **34**, 187–220 (1972).
6) Cutler, S. J. and Ederer, F. Maximum utilization of the life table method in analyzing survival. *J. Chronic Dis.*, **8**, 699–712 (1958).
7) Peto, R., Pike, M. C. and Armitage, N. E. Design and analysis of randomized clinical trials requiring prolonged observation of each patient II. Analysis and example. *Br. J. Cancer*, **35**, 1–39 (1977).
8) Shapiro, S. Evidence on screening for breast cancer from a randomized trial. *Cancer*, **36**, 2772–2782 (1977).
9) Tabar, L., Fagerberg, C. J. G., Gad, A., Baldetorp, L., Holmberg, L. H., Grontoft, O., Ljungquist, U., Lundstrom, B., Manson, J. C., Eklund, G., Pettersson, F. and Day, N. E. Reduction in mortality from breast cancer after mass screening with mammography. *Lancet*, **i**, 829–832 (1985).
10) Oshima, A., Hirata, N., Ubukata, T., Umeda, K. and Fujimoto, I. Evaluation of a mass screening program for stomach cancer with a case-control study design. *Int. J. Cancer*, **38**, 829–833 (1986).
11) Sobue, T., Suzuki, T., Hashimoto, S., Yokoi, N. and Fujimoto, I. A case-control study of the effectiveness of cervical cancer screening in Osaka, Japan. *Jpn. J. Cancer Res.*, **79**, 1269–1275 (1988).
12) Kuroishi, T., Hirose, K. and Tominaga, S. An epidemiological evaluation of the efficacy of mass screening for stomach cancer in Japan with special reference to the comparisons of the trend in mortality from stomach cancer between the high coverage-rate areas for stomach cancer screening and the control areas. *J. Gastroenterol. Mass Surv.*, **69**, 51–56 (1985) (in Japanese).
13) Kuroishi, T., Hirose, K. and Tominaga, S. Evaluation of the efficacy of mass screening for uterine cancer in Japan. *Jpn. J. Cancer Res.*, **77**, 399–405 (1986).
14) Morimoto, T., Komaki, K. Oshimo, K., Yamakawa, T., Mitsuyama, N., Tanaka, T. and Monden, Y. Breast cancer detected by mass screening using physical examination. *Jpn. J. Surg.*, **17**, 377–381 (1987).
15) Ishida, T., Yokoe, T., Ogawa, T., Kurosumi, M., Kurebayashi, J., Yoshida, M., Yamada, I., Iino, Y. and Izuo, M. Mass screening for breast cancer in Gunma Prefecture — the results for 8 years and future problems. *J. Jpn. Soc. Cancer Ther.*, **24**, 2400–2410 (1989) (in Japanese).
16) Abe, R. Modality as mass screening for breast cancer. *Image Technol. Inform. Display*, **22**, 419–423 (1990) (in Japanese).
17) Rodes, R. D., Lopez, M. J., Pearson, D. K., Blackwell, C. W. and Lankford, H. D. The impact of breast cancer screening on survival — a 5- to 10-year follow-up study. *Cancer*, **57**, 581–585 (1986).
18) Kido, C., Endo, T. and Hotta, K. DMR in mass screening for breast cancer. *Image Technol. Inform. Display*, **22**, 429–434 (1990) (in Japanese).
19) Terada, H. and Shinya, M. Development in technique and equipments of mammography. *Image Technol. Inform. Display*, **22**, 435–441 (1990) (in Japanese).