Effect of Physical Activity on Breast Cancer Risk: Findings of the Japan Collaborative Cohort Study

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Abstract

Purpose: **This study aimed to examine prospectively the association between physical activity and breast cancer risk in a non-Western population.**
Methods: **We analyzed data from the Japan Collaborative Cohort Study, which included 30,157 women, ages 40 to 69 years at baseline (1988-1990), who reported no previous history of breast cancer, and provided information on their walking and exercise habits. The subjects were followed prospectively from enrollment until 2001 (median follow-up period, 12.4 years). Breast cancer incidence during this period was confirmed using records held at population-based cancer registries. The Cox proportional hazards model was used to estimate the hazard ratio (HR) for the association of breast cancer incidence with physical activity.**
Results: **During the 340,055 person-years of follow-up, we identified 207 incident cases of breast cancer. The most physically active group (who walked for ≥1 hour per day and exercised for ≥1 hour per week) had a lower risk of breast cancer (HR, 0.45; 95% confidence interval, 0.25-0.78) compared with the least active group after adjusting for potential confounding factors. The inverse association of exercise on breast cancer was stronger among those who walked for ≥1 hour per day than those who walked for <1 hour per day (*P* = 0.042). These results were not significantly modified by menopausal status or body mass index (BMI).**
Conclusions: **Our analysis provided evidence that physical activity decreased the risk of breast cancer. Walking for 1 hour per day and undertaking additional weekly exercise both seemed to be protective against breast cancer, regardless of menopausal status or BMI.** (Cancer Epidemiol Biomarkers Prev 2008;17(12):3396–401)

Introduction

Since the early 1990s, breast cancer has been the most commonly diagnosed cancer, even among Japanese women (1). The continuous increase in breast cancer incidence during recent decades has been an important public health concern in Japan, and there has been growing interest in physical activity as a means of primary prevention. Worldwide, numerous epidemiologic studies have reported associations between physical activity and cancer risk, with most observing a protective effect. Reviews published in 2002 concluded that there was sufficient evidence to support the role of physical activity in preventing breast cancer (2, 3). A systematic review published in 2007 (4) showed a decreased relative risk (<0.8) associated with leisure activities in 8 of 17 cohort studies (5-12), whereas the remaining 9 reported no association (13-21). Three more-recent cohort studies supported the risk reduction (22-24), whereas one found no evidence of a protective effect of physical activity on breast cancer (25). In addition to the 20% to 40% overall risk reduction of breast cancer among the more physically active women (2), the effects of menstrual characteristics, obesity, use of sex hormones, hormone-receptor status, and immune function have also been discussed in previous reports (24, 26, 27). However, these have been based on data from Western populations, and to our knowledge there have been no prospective reports from Asia. Different factors might influence Asian populations, as their characteristics (such as breast cancer incidence, physical activity, and body size) tend to differ from those of Western populations. Here, we analyzed data from a large-cohort study, the Japan Collaborative Cohort (JACC) Study, to examine the relationship between physical activity and breast cancer with a particular emphasis on the interactions with other risk factors, such as menopausal status and obesity.

Materials and Methods

Study Population. The present analysis was based on data from the JACC Study. This prospective cohort study evaluated the cancer risk associated with lifestyle factors

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among the Japanese population. At baseline (1988-1990), 110,792 subjects (46,465 men and 64,327 women), ages 40 to 79 y, were enrolled from 45 areas throughout Japan. All of the participants were subsequently followed up for all-cause mortality. Of the women in the baseline cohort, 34,086 lived in the 22 areas where data on both cancer incidence and physical activity were available. The JACC Study has been described in detail elsewhere (28, 29). Informed consent for participation was obtained from all individuals, with the exception of those in a few study areas where informed consent was provided at the group level, after the aims and data confidentiality had been explained to community leaders. The Ethics Board of Nagoya University School of Medicine, Japan, approved the JACC Study protocol.

Physical Activity Assessment. A self-administered questionnaire was used to obtain information on physical activity at baseline (30). The items covered included amount of time spent walking, amount of time spent exercising, and physical activity at the work place. Time spent walking daily was classified into three categories (<30 min, 30-59 min, and ≥1 h), as was time spent exercising (never or seldom, 1-2 h/wk, ≥3 h/wk). The validity of the estimates of time spent participating in sports and leisure activities was examined in a sample of the baseline subjects, suggesting that measuring physical activity level with the single-item question may be appropriate for establishing baseline data that reflect long-term physical activity in a large-scale cohort study (30, 31). We did not analyze the metabolic equivalent intensity, because of a lack of information on the strength of the exercise.

Other Variables. Information on additional potential breast cancer risk factors, such as family history, body mass index (BMI), tobacco and alcohol use, age at menarche, marital status, parity, age at birth of first child, menopausal status, and hormone use, was collected via the baseline questionnaire.

Follow-up and Identification of Breast Cancer Cases. The study participants were followed up from the time of enrollment until 2001, excluding five areas in which they were halted earlier. During this period, population registry data from each municipality were used to ascertain the residential and vital status of the participants. In Japan, the registration of death is required by the Family Registration Law, theoretically providing complete mortality data. Breast cancer incidence was confirmed mainly through the records of the population-based cancer registries in each area. During the study period, only 1,189 (3.9%) of the subjects were lost to follow-up due to moving out of the given study areas. The proportion of death-certificate-only cases was 6.3% (13 of 207). The mortality-to-incidence ratio for breast cancer was 0.26 (50 of 194) in the cohort covered by the cancer registries, which was within the range calculated using the available data from population-based cancer registries in Japan (0.20-0.30; ref. 32). We expect 37.4 breast cancer incidence cases who cannot be found from the cancer registries. The present analysis excluded 246 women who reported a previous diagnosis of breast cancer and 3,683 women who did not provide information on physical activity at baseline. Thus, a total of 30,157 women were included in the present analysis.

Statistical Analysis. For all participants, the person-years of follow-up was calculated as the time from enrollment until the diagnosis of breast cancer, death from any cause, moving out of the study area, or the end of follow-up, whichever occurred first. For the breast cancer cases ascertained by death-certificate-only, the person-years of follow-up were calculated from the time of enrollment until the time of death from breast cancer. Those individuals who died from causes other than breast cancer (n = 2,518) or who moved out of the study areas were treated as censored cases. We used Cox proportional hazards models to estimate the hazard ratios (HR) and 95% confidence intervals (95% CI) for the association of breast cancer incidence with physical activity. We evaluated the relationship using two models: an age-adjusted model (using 5-y age groups), and a multivariable model with adjustments for age, BMI (<22.0 kg/m^2, 22.0-23.9 kg/m^2, 24.0-25.9 kg/m^2, ≥26.0 kg/m^2, or unknown), alcohol drinking (never, past, current, or unknown), age at menarche (<15 y, 15-16 y, ≥17 y, or unknown), education level (attended school until the age of <16 y, 16-18 y, ≥19 y, or unknown), parity (nulliparous, 1 birth, 2-3 births, ≥4 births, or unknown), age at birth of first child (<22 y, 22-23 y, 24-25 y, ≥26 y, or unknown), use of exogenous female hormone (yes, no, or unknown), family history of breast cancer in a first-degree relative (yes, no, or unknown), menopausal status (premenopausal or postmenopausal), and menopausal age for postmenopausal women (<45 y, 45-49 y, ≥50 y, or unknown). In this study, those who provided menopausal age or who were at the average age at menopause, i.e., ≥49 y at baseline, were treated as postmenopausal women, and only those who were <49 y without information of menopausal age were treated as premenopausal women. Each ''unknown'' category included 5% to 9% of all women. All analyses were stratified by six study areas (Hokkaido and Tohoku, Kanto, Chubu, Kinki, Chugoku, and Kyushu). Trend tests were done for category-based scores, which were assessed by allocating values ranging from 1 to 3 to each individual according to the selected physical activity variables.

To estimate the interaction of time spent walking and time spent exercising, we recategorized the subjects into four groups using the following cutoff points for physical activity: daily walking for <1 h or ≥1 h, and weekly exercising for <1 h or ≥1 h. Furthermore, the HR for the most active group (those who walked for ≥1 h/d and exercised for ≥1 h/wk) compared with the other groups was estimated according to menopausal status and BMI (<24 or ≥24 kg/m^2), and we examined the interaction between physical activity and these factors (Table 5). We used a BMI of 24 kg/m^2 instead of 25 kg/m^2 as a cutoff point for overweight. That was because there were only 47 cases for BMI ≥24 kg/m^2, which were too few to discuss interaction. For instance, we estimated the two HRs for physical activity among women who were premenopausal and postmenopausal at baseline, and then the P value for the interaction term of menopausal status and physical activity was calculated to test the difference between these HRs. We repeated the analysis after excluding the initial 2 y of follow-up, during which 37 cases of breast cancer were diagnosed. All of the P values were two-sided, with P < 0.05 indicating statistical significance. All of the analyses were done with SAS version 9.1 (SAS Institute, Inc.).

Table 1. Baseline characteristics associated with age in the JACC Study

Characteristics	Age group				Total
	40-49 y	50-59 y	60-69 y	70-79 y	
Number, *n* (row %)	7,561 (25.1)	9,361 (31.0)	9,098 (30.2)	4,137 (13.7)	30,157 (100.0)
Time spent walking per day					
Never or seldom, *n* (%)	868 (11.5)	1,013 (10.8)	807 (8.9)	403 (9.7)	3,091 (10.2)
Around 30 min, *n* (%)	1,393 (18.4)	1,650 (17.6)	1,794 (19.7)	876 (21.2)	5,713 (18.9)
30-59 min, *n* (%)	1,584 (20.9)	1,989 (21.2)	1,945 (21.4)	956 (23.1)	6,474 (21.5)
≥1 h, *n* (%)	3,716 (49.1)	4,709 (50.3)	4,552 (50.0)	1,902 (46.0)	14,879 (49.3)
Time spent exercising per wk					
Never or seldom, *n* (%)	5,890 (77.9)	7,365 (78.7)	6,591 (72.4)	2,842 (68.7)	22,688 (75.2)
1-2 h, *n* (%)	1,176 (15.6)	1,298 (13.9)	1,412 (15.5)	617 (14.9)	4,503 (14.9)
3-4 h, *n* (%)	338 (4.5)	399 (4.3)	572 (6.3)	306 (7.4)	1,615 (5.4)
≥5 h, *n* (%)	157 (2.1)	299 (3.2)	523 (5.7)	372 (9.0)	1,351 (4.5)

NOTE: Mean (SD) or %, calculated for participants with complete physical activity data.

Results

The average age at baseline was 57.6 ± 10.1 years, and the median follow-up time was 12.4 years. During the 340,055 person-years of follow-up, we identified 207 incident cases of breast cancer. The annual incidence of breast cancer in the cohort per 1,000 women was 0.61. Table 1 shows the distributions of physical activity according to age. Time spent walking was distributed similarly in the four age groups, with ~50% of the subjects walking for ≥1 hour per day. By contrast, for time spent exercising and physical activity at the work place, the older the subjects, the more physically active they tended to be. Regardless of the age group, more than two thirds of the participants never or seldom exercised.

Table 2 presents the risk of breast cancer in relation to physical activity. After adjusting for potential confounding factors, the HR was marginally decreased among those who walked for ≥1 hour per day (HR, 0.73; 95% CI, 0.53-1.01). However, those who exercised for ≥3 hours per week were not statistically decreased (HR, 0.85; 95% CI, 0.51-1.40). The *P* value for the linear trend of time spent walking was 0.043, which indicated that the dose-response effect of time spent walking and breast cancer risk was significant. The adjusted HR for those who walked for ≥1 hour compared with the rest of the women was significantly different (HR, 0.70; 95% CI, 0.53-0.93), although that for those who exercised for ≥3 hours per week was not significant (HR, 0.83; 95% CI, 0.59-1.16).

To investigate the joint effect of walking and exercise, we recategorized the data using the following cutoff points for physical activity: daily walking for <1 hour and exercising for <1 hour per week. Table 3 shows the mean values and distributions of risk factors for breast cancer according to the walking and exercise time categories. The subjects who walked and exercised more tended to be older and to drink more alcohol. The BMI values did not significantly differ between categories (range, 22.7-22.8 kg/m^2).

Table 4 shows the HRs of breast cancer associated with the joint effect of time spent walking and time spent exercising. The most physically active group (those who walked for ≥1 hour per day and exercised for ≥1 hour per week) had a lower risk of breast cancer (HR, 0.45; 95% CI, 0.25-0.78) compared with the least active group after adjusting for potential confounding factors. A significant interaction ($P = 0.042$) was observed between time spent walking and time spent exercising, meaning that the combined effect of exercise and walking on breast cancer was significant.

The HR of the most physically active group compared with the rest of the women was estimated for the subgroups according to menopausal status and BMI in Table 5, to examine the effects modification of these factors on the association between physical activity and breast cancer onset. The marginal inverse association was

Table 2. HR of breast cancer associated with physical activity in the JACC study

Physical activity	Cases	Person-years	Age adjusted	Multivariate*
			HR (95% CI)	HR (95% CI)
Time spent walking per day				
<30 min	69	96,752	1.00 (Reference)	1.00 (Reference)
30−59 min	56	71,411	1.14 (0.71 − 1.84)	1.13 (0.80 − 1.61)
≥1 h	82	171,892	0.70 (0.51 − 0.97)	0.73 (0.53 − 1.01)
P for trend			0.021	0.043
Time spent exercising per week				
Never or seldom	161	255,829	1.00 (Reference)	1.00 (Reference)
1−2 h	29	51,043	0.87 (0.59 − 1.30)	0.83 (0.56 − 1.23)
≥3 h	17	33,183	0.87 (0.53 − 1.45)	0.85 (0.51 − 1.40)
P for trend			0.45	0.33

*Adjusted for age, BMI, alcohol drinking, age at menarche, education level, parity, age at birth of first child, use of exogenous female hormone, family history of breast cancer in a first-degree relative, menopausal status, and menopausal age for postmenopausal women.

Table 3. Baseline characteristics associated with physical activity in the JACC study

Characteristics	Time spent exercising <1 h/wk		Time spent exercising ≥1 h/wk	
	Time spent walking per day		Time spent walking per day	
	<1 h	≥1 h	<1 h	≥1 h
Number, *n* (row %)	11,864 (39.3)	10,824 (35.9)	3,414 (11.3)	4,055 (13.4)
BMI, mean ± SD (kg/m^2)	22.8 ± 3.2	22.7 ± 3.0	22.8 ± 3.0	22.7 ± 2.9
Age at baseline, mean ± SD, y	57.5 ± 10.3	56.8 ± 9.6	58.5 ± 10.3	59.2 ± 10.4
Age at menarche, mean ± SD, y	14.8 ± 1.8	14.9 ± 1.8	14.8 ± 1.8	14.9 ± 1.8
Age at birth of first child, mean ± SD, y	25.2 ± 3.3	25.0 ± 3.3	25.1 ± 3.2	24.9 ± 3.1
Age at menopause, mean ± SD, y	48.7 ± 4.8	48.6 ± 4.6	48.8 ± 4.7	48.9 ± 4.5
Age of the end of education, mean ± SD, y	16.6 ± 2.1	16.5 ± 2.1	16.9 ± 2.2	16.7 ± 2.1
Postmenopausal, *n* (%)	8,946 (75.4)	8,176 (75.5)	2,657 (77.8)	3,225 (79.5)
Nulliparous, *n* (%)	612 (5.2)	387 (3.6)	142 (4.2)	163 (4.0)
Not married, *n* (%)	223 (2.0)	120 (1.2)	65 (2.1)	42 (1.1)
Exogenous female hormone use, *n* (%)	580 (5.4)	474 (4.8)	191 (6.2)	207 (5.7)
Family history of breast cancer,* *n* (%)	191 (1.6)	159 (1.5)	63 (1.9)	65 (1.6)
Current smoker, *n* (%)	606 (5.6)	556 (5.7)	133 (4.3)	183 (5.0)
Current drinker, *n* (%)	2,594 (23.1)	2,447 (24.0)	906 (27.9)	1,122 (29.4)

NOTE: Mean (SD) or %, calculated for participants with complete physical activity data.
*In a first-degree relative.

observed in each subgroup, and no significant interaction was observed. This suggests that the inverse association was not modified by these factors. Similar results were found after excluding the initial 2 years of follow-up, during which 37 cases of breast cancer were diagnosed.

Discussion

Our prospective analysis of the relationship between physical activity and breast cancer in Japanese women revealed a significant inverse association. In particular, the combined effect of walking and exercise was stronger than that expected based on the individual effects. Moreover, the combined protective effect of walking and exercise was not modified significantly by menopausal status or BMI. This suggests that physical activity has a protective effect regardless of menopausal status or weight. Previous studies of Western populations have provided convincing evidence of an inverse association between physical activity and breast cancer risk (2, 3), as supported by a recent systematic review (4). Adding more recent cohort studies (22-25), 10 of 21 showed a significantly decreased breast cancer risk associated with physical activity. Despite the comparatively lower incidence of breast cancer in Japan (1), an inverse association between physical activity and breast cancer incidence has also been observed, which was consistent with the findings of previous case-control studies in Japan (33-35).

The present study showed an interactive effect of walking and exercise. This could be explained in several ways. For instance, multiple types of exercise might work more effectively than a single type of exercise, the effect of physical activity might be quadratic, or walkers might tend to exercise more intensely. Whatever the reason, our results indicate that walking for ≥1 hour per day should initially be recommended, and additional weekly exercise should be undertaken to improve the protective effect against breast cancer.

In the present study, menopausal status and BMI did not affect the relationship between physical activity and breast cancer. Of the two, the modifying effect of menopausal status is the more controversial. Among the previous cohort studies that have analyzed this association according to menopausal status, only two have observed a significantly decreased breast cancer risk among premenopausal women (11, 22), and the evidence is weaker among premenopausal women (5, 10, 17). This difference might be partly due to the way in which menopause has been treated in the analyses. All of the studies, including the present one, reporting a protective effect of physical activity among premenopausal women have used only baseline menopausal status and have not updated this measure. By contrast, a study that found no association did update the menopausal status (19), and menopause was included as one of its end points.

Compared with menopausal status, the effect modification of BMI on the association between physical

Table 4. HR of breast cancer associated with physical activity in the JACC study

Physical activity		Cases	Person-years	Age adjusted	Multivariate*
Time spent walking (h/d)	Time spent exercising (h/wk)			HR (95% CI)	HR (95% CI)
<1	<1	93	130,279	1.00 (Reference)	1.00 (Reference)
≥1	<1	68	125,550	1.18 (0.79 − 1.77)	1.13 (0.75 − 1.69)
<1	≥1	32	37,885	0.76 (0.56 − 1.04)	0.82 (0.60 − 1.12)
≥1	≥1	14	46,342	0.42 (0.24 − 0.74)	0.45 (0.25 − 0.78)
P for interaction				0.035	0.041

*Adjusted for age, BMI, alcohol drinking, age at menarche, education level, parity, age at birth of first child, use of exogenous female hormone, family history of breast cancer in a first-degree relative, menopausal status, and menopausal age for postmenopausal women.

Table 5. HR of breast cancer among the most physically active group compared with the rest of the women by subgroup of menopausal status and BMI in the JACC study

Subgroup	Age adjusted	Multivariate*
	HR (95% CI)	HR (95% CI)
Menopausal status		
Premenopausal	0.14 (0.02 – 0.97)	0.13 (0.02 – 0.91)
Postmenopausal	0.53 (0.29 – 0.96)	0.53 (0.29 – 0.96)
P for interaction	0.524	0.528
BMI (kg/m^2)		
<24	0.43 (0.20 – 0.91)	0.42 (0.19 – 0.90)
≥24	0.45 (0.18 – 1.10)	0.44 (0.18 – 1.09)
P for interaction	0.940	0.949

*Adjusted for age, BMI, alcohol drinking, age at menarche, education level, parity, age at birth of first child, use of exogenous female hormone, family history of breast cancer in a first-degree relative, menopausal status, and menopausal age for postmenopausal women.

activity and breast cancer risk has been more consistent, as previous studies have failed to show general effects (5, 6, 8-10, 13, 14, 16, 18, 19, 21). These findings suggest that the effect of physical activity is independent of menopausal status (despite the possibility of a less precise effect among premenopausal women) and BMI. Therefore, the recommendation to undertake physical activity to prevent breast cancer does not need to be altered according to differences in these factors.

A major strength of the present study is its prospective design, which might avoid the recall bias that is possible in case-control studies. Moreover, information on other risk factors for breast cancer was included, and potential confounding factors were controlled for in the analyses when examining the association.

Our study had some limitations that should be considered when interpreting the results. First, because we used only a simple questionnaire at baseline, neither metric equivalent nor updated values were available to evaluate physical activity. In general, assessing physical activity in epidemiologic studies is difficult, which might explain the heterogeneous results observed across studies of its association with breast cancer (36). Although it is possible that the reported levels might have overestimated or underestimated the actual physical activity, the information was collected before diagnosis and should not have differed according to the end point status. Thus, the misclassification of physical activity in the present study for both reasons is nondifferential. It means the estimated HRs tend to be close to the null, and true HRs should be smaller due to the misclassification. In addition, because more than two thirds of the women in our cohort never or seldom exercised, we expect less serious misclassification. Second, updated information on menopausal status was lacking, which could modify the relationship between physical activity and breast cancer. Thus, from an etiologic viewpoint, the misclassification of menopausal status at the onset of breast cancer should be important. However, from the viewpoint of cancer prevention, the menopausal status at cancer onset is comparatively less important, and the HR could be naturally interpreted for premenopausal women at baseline. Third, misclassification of menopausal status at baseline should also be considered. However, the point estimate of the HR among premenopausal women was smaller than that among postmenopausal women, which could not be explained from misclassification. In addition, the results were not essentially changed when we removed women who were 47 to 50 years old from the premenopausal group. More studies are needed of premenopausal women in larger subjects.

In summary, our analysis provided evidence that physical activity decreased the risk of breast cancer among Japanese women. Another encouraging finding of this study is that the effect of physical activity on breast cancer risk is not modified by menopausal status and BMI. We recommend walking for 1 hour per day along with additional weekly exercise to protect against breast cancer, regardless of menopausal status and BMI.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Appendix 1. The Japan Collaborative Cohort Study Group

The present members of the JACC Study and their affiliations are as follows: Dr. Akiko Tamakoshi (present chairman of the study group), Aichi Medical University School of Medicine; Dr. Mitsuru Mori, Sapporo Medical University School of Medicine; Dr. Yutaka Motohashi, Akita University School of Medicine; Dr. Ichiro Tsuji, Tohoku University Graduate School of Medicine; Dr. Yosikazu Nakamura, Jichi Medical School; Dr. Hiroyasu Iso, Institute of Community Medicine, University of Tsukuba; Dr. Haruo Mikami, Chiba Cancer Center; Dr. Yutaka Inaba, Juntendo University School of Medicine; Dr. Yoshiharu Hoshiyama, University of Human Arts and Sciences Graduate School; Dr. Hiroshi Suzuki, Niigata University Graduate School of Medical and Dental Sciences; Dr. Hiroyuki Shimizu, Gifu University School of Medicine; Dr. Hideaki Toyoshima, Nagoya University Graduate School of Medicine; Dr. Shinkan Tokudome, Nagoya City University Graduate School of Medical Sciences; Dr. Yoshinori Ito, Fujita Health University School of Health Sciences; Dr. Shuji Hashimoto, Fujita Health University School of Medicine; Dr. Shogo Kikuchi, Aichi Medical University School of Medicine; Dr. Kenji Wakai, Nayoga University Graduate School of Medicine; Dr. Akio Koizumi, Graduate School of Medicine and Faculty of Medicine, Kyoto University; Dr. Takashi Kawamura, Kyoto University Center for Student Health; Dr. Yoshiyuki Watanabe and Dr. Tsuneharu Miki, Kyoto Prefectural University of Medicine Graduate School of Medical Science; Dr. Chigusa Date, Faculty of Human Environmental Sciences, Mukogawa Women's University; Dr. Kiyomi Sakata, Wakayama Medical University; Dr. Takayuki Nose, Tottori University Faculty of Medicine; Dr. Norihiko Hayakawa, Research Institute for Radiation Biology and Medicine, Hiroshima University; Dr. Takesumi Yoshimura, Institute of Industrial Ecological Sciences, University of Occupational and Environmental Health, Japan; Dr. Akira Shibata, Kurume

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The past investigators of the study group were listed in ref. 28 except for the following eight members (affiliations are those at the time they participated in the study): Dr. Takashi Shimamoto, Institute of Community Medicine, University of Tsukuba; Dr. Heizo Tanaka, Medical Research Institute, Tokyo Medical and Dental University; Dr. Shigeru Hisamichi, Tohoku University Graduate School of Medicine; Dr. Masahiro Nakao, Kyoto Prefectural University of Medicine; Dr. Takaichiro Suzuki, Research Institute, Osaka Medical Center for Cancer and Cardiovascular Diseases; Dr. Tsutomu Hashimoto, Wakayama Medical University; Dr. Teruo Ishibashi, Asama General Hospital; and Dr. Katsuhiro Fukuda, Kurume University School of Medicine.

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