1.34(0.94-1.90;p=0.08)であった。牛乳・乳製品 1 日 100ｇ摂取増加毎のハザード比は、女性において循環器疾患死亡 0.86(0.74-0.99)、心疾患死亡 0.73(0.52-1.03)、脳血管疾患死亡 0.81(0.65-1.01)で低下傾向にあった。男性では有意な関連は見られなかった。

【結論】

牛乳・乳製品の摂取は日本において女性で循環器疾患死亡と負の関連があった。

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Original Article

Consumption of Dairy Products and Death From Cardiovascular Disease in the Japanese General Population: The NIPPON DATA80

Imako Kondo[1,2], Toshiyuki Ojima[2], Mieko Nakamura[2], Shinya Hayasaka[2], Atsushi Hozawa[3], Shigeyuki Saitoh[4], Hirofumi Ohnishi[4], Hiroshi Akasaka[4], Takehito Hayakawa[5], Yoshitaka Murakami[6], Nagako Okuda[7], Katsuyuki Miura[8], Akira Okayama[9], and Hirotsugu Ueshima[8,10], for the NIPPON DATA80 Research Group

[1]Faculty of Health Promotional Sciences, Hamamatsu University, Hamamatsu, Shizuoka, Japan
[2]Department of Community Health and Preventive Medicine, Hamamatsu University School of Medicine, Hamamatsu, Shizuoka, Japan
[3]Department of Preventive Medicine and Epidemiology, Tohoku Medical Megabank Organization, Sendai, Japan
[4]Second Department of Internal Medicine, Sapporo Medical University School of Medicine, Sapporo, Japan
[5]Department of Hygiene and Preventive Medicine, Fukushima Medical University, Fukushima, Japan
[6]Department of Medical Statistics, Shiga University of Medical Science, Otsu, Japan
[7]Department of Nutrition Epidemiology, National Institute of Health and Nutrition, Tokyo, Japan
[8]Department of Health Science, Shiga University of Medical Science, Otsu, Japan
[9]The First Institute for Health Promotion and Health Care, Japan Anti-Tuberculosis Association, Tokyo, Japan
[10]Lifestyle-Related Disease Prevention Center, Shiga University of Medical Science, Otsu, Japan

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ABSTRACT

Background: Recent Western studies show an inverse association between milk and dairy product intake and cardiovascular disease (CVD). We studied the association between consumption of milk and dairy products and CVD death in Japan.

Methods: Men and women aged 30 years or older were followed for 24 years. All had participated in a national nutrition survey in 300 health districts throughout Japan in 1980. The Cox proportional hazards model was used to assess mortality risk according to tertiles of milk and dairy product intake, with the high consumption group as reference. Hazard ratios (HRs) per 100-g/day increase in consumption were also estimated.

Results: During the 24-year follow-up period, there were 893 CVD deaths, 174 deaths from coronary heart disease (CHD), and 417 stroke deaths among 9243 participants. For women, the HRs for death from CVD, CHD, and stroke in the low consumption group were 1.27 (95% CI: 0.99–1.58; P for trend = 0.045), 1.67 (0.99–2.80; $P = 0.02$), and 1.34 (0.94–1.90; $P = 0.08$), respectively, after adjustment for age, body mass index, smoking status, alcohol drinking habits, history of diabetes, use of antihypertensives, work category, and total energy intake. With each 100-g/day increase in consumption of milk and dairy products, HRs tended to decrease for deaths from CVD (HR, 0.86; 95% CI, 0.74–0.99), CHD (0.73; 0.52–1.03), and stroke (0.81; 0.65–1.01) in women. No significant association was observed in men.

Conclusions: Consumption of milk and dairy products was inversely associated with CVD death among women in Japan.

Key words: dairy products; cardiovascular disease; mortality; blood pressure; coronary heart disease

INTRODUCTION

In recent years, findings from several cohort studies have suggested that intake of dairy products is inversely associated with the risk of hypertension,[1,2] cardiovascular disease (CVD),[3] coronary heart disease (CHD),[4,5] and stroke.[5–7] In addition, a meta-analysis[8] of 4 cohort studies from Western countries indicated that milk intake may be inversely associated with overall CVD risk.

In Japan, consumption of milk and dairy products is recommended to ensure nutritional balance, especially adequate intake of calcium. New dietary guidelines in

Address for correspondence. Prof. Toshiyuki Ojima, Department of Community Health and Preventive Medicine, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsu 431-3192, Japan (e-mail: ojima@hama-med.ac.jp).

Japan[9] encourage individuals to obtain sufficient calcium by consuming milk and dairy products, green and yellow vegetables, tofu, and small fish. Similarly, the Japanese Food Guide Spinning Top,[10] a dietary balance guideline for Japanese, recommends consumption of 2 servings of milk and dairy products (200 ml of milk, equivalent to 200 mg of calcium) per day for adults. However, current consumption of milk and dairy products in Japan is much lower than this recommended level. The National Nutrition Survey, Japan 2008 (NNSJ 2008)[11] found that the average daily consumption of milk and dairy products by adults was 89.0 g, which is much lower than in Western countries.

Most of the above-mentioned studies that showed an inverse association with CVD were conducted in Western countries, where milk and dairy product consumption is much higher than in Japan. Only 2 cohort studies[6,7] of the association between dairy calcium intake and CVD risk have been done in Japan. In these 2 studies, participants were followed for about 10 to 13 years.

We analyzed the association of milk and dairy product consumption with CVD death in a representative sample of Japanese who were followed for 24 years.

METHODS

Dataset

For data analysis, we used an integrated dataset from the NIPPON DATA80 (National Integrated Project for Prospective Observation of Non-communicable Disease And its Trends in the Aged). The participants in this cohort were the same as those in the 1980 National Survey on Circulatory Disorders.[12] A total of 10 546 community-based men and women aged 30 years or older in 300 randomly selected districts throughout Japan participated in the survey, which consisted of history-taking, physical examinations, blood tests, and self-administered questionnaires on lifestyle. Details of NIPPON DATA80 have been described previously.[13–15]

The NIPPON DATA80 cohort also participated in the National Nutrition Survey, Japan, conducted in the same year (NNSJ1980),[16] and data on nutritional intake per individual were added to the dataset from the results of NNSJ1980. Nutrient intake was estimated using weighed diet records for 3 consecutive days during which there were no special events. Weekends and holidays were avoided for the survey. Registered dietitians at public health centers in each district, who were specially trained in dietary interviews, visited participants' homes at least once during the survey. Diet records were thoroughly reviewed by the registered dietitians. Nutrient intake was calculated using the updated Standard Tables for Food Composition in Japan, Fourth Edition, with matched fatty acid values and micronutrients. Food and nutrient intakes of each household member were estimated by dividing the household intake data from NNSJ1980,[16] using average intake by sex and age group calculated from NNSJ1995.[17] The average intake of NNSJ1995[17] was calculated using a method that combined household-based weighed diet records with an approximation of proportions by which family members shared each dish or food in the household. For each participant, means of the estimated individual food and nutrient intakes for 3 consecutive days were used in the analyses. The details of the methods used in the nutritional survey and the estimation of individual intake have been described elsewhere.[18]

Baseline variables

Height in stocking feet and weight in light clothing were measured. Body mass index (BMI) was calculated as weight (kg) divided by the square of the height (m). Blood pressure was measured on the right arm of seated participants by trained observers using a standard mercury sphygmomanometer. Serum total cholesterol was analyzed using an autoanalyzer (SMA12/60; Technicon, Tarrytown, NY, USA) at 1 central laboratory (present name: Osaka Medical Center for Health Science and Promotion). Since April 1975, the precision and accuracy of the cholesterol measurements in the laboratory have been certified by the Centers for Disease Control–National Heart, Lung, and Blood Institute (CDC-NHLBI) Lipid Standardization Program of the Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia.

Information on history of CVD and/or diabetes, use of antihypertensives, smoking status, drinking habits, and work category was obtained from interviewer-administered questionnaires. Smoking status was classified as never-smoker, current smoker of 20 or fewer cigarettes/day, current smoker of 21 or more cigarettes/day, and ex-smoker. Alcohol drinking habit was classified as never-drinker, occasional drinker, daily drinker, and ex-drinker. Work category was classified as manager/professional and non-manager/professional. Milk and dairy product consumption per day was used to allocate participants into 3 groups by sex-specific tertiles. In men, daily consumption of 42.4 g or less was considered low intake, 42.5 to 81.5 as moderate intake, and 81.6 g or more as high intake. In women, the respective levels were 53.6 g or less, 53.7 to 105.6 g, and 105.7 g or more. In the present study, data on milk and dairy products cannot be divided into type of milk and dairy products. In 1980, almost all (93%) milk and dairy product consumption was in the form of milk.[16]

Outcome

Outcome data obtained from follow-up surveys until 2004 were analyzed in this study. Underlying causes of death were coded for Japanese National Vital Statistics according to the Ninth International Classification of Disease (ICD-9) until the end of 1994 and according to the 10th International Classification of Disease (ICD-10) from the beginning of

1995. Permission to use National Vital Statistics was obtained from the Management and Coordination Agency of the Government of Japan. The respective codes for ICD-9 and ICD-10 were as follows: CVD—393 to 459 (ICD-9) and I00 to I99 (ICD-10); CHD—410 to 414 (ICD-9) and I20 to I25 (ICD-10); stroke—430 to 438 (ICD-9) and I60 to I69 (ICD-10). Approval for this study was obtained from the Institutional Review Board of Shiga University of Medical Science.

Statistical analyses

We excluded participants with a total energy intake less than 500 kcal/day or greater than 5000 kcal/day ($n = 139$), those lost to follow-up ($n = 909$), those with a past history of CVD ($n = 280$), and those with missing data on height, weight, blood pressure, serum total cholesterol, history of diabetes, smoking status, or alcohol drinking habit ($n = 48$).

First, variables were compared between tertiles of milk and dairy product consumption. One-way analysis of variance was used to compare means of milk and dairy product consumption, age, BMI, systolic blood pressure, diastolic blood pressure, serum total cholesterol concentration, total energy intake, and consumption of foods (vegetables, fruit, fish and shellfish, meat and poultry, eggs, fat and oil, and salt) among tertiles by sex. The chi-square test was used to compare the categorical variables of history of diabetes, use of antihypertensives, smoking status, alcohol drinking habit, and work category among the tertiles by sex. Analysis of covariance was used to compare age-adjusted means for milk and dairy product consumption, BMI, systolic blood pressure, diastolic blood pressure, serum total cholesterol concentration, total energy intake, and consumption of foods among tertiles by sex.

Second, crude mortality of CVD, CHD, and stroke among tertiles was calculated, and the Cox proportional hazards model was then used to estimate hazard ratios (HRs) of CVD, CHD, and stroke mortality associated with milk and dairy product consumption by sex. HRs and their 95% CIs for the moderate and low milk and dairy product intake groups were calculated using the high intake group as a reference. The trend tests were performed using the Cox proportional hazards model, with the milk and dairy consumption tertiles analyzed as a continuous variable. Also, HRs per 100-g/day increase in milk and dairy product consumption were estimated in both sexes.

We constructed 3 models: age was adjusted in Model 1; BMI (sex-specific tertiles), alcohol drinking habit (never, occasional, daily, and ex-drinker), smoking status (never, current smoker of ≤20 and ≥21 cigarettes/day, and ex-smoker), history of diabetes (yes, no), use of antihypertensives (yes, no), work category (manager/professional, non-manager/professional) as dummy variables, and total energy intake as a continuous variable, were further adjusted in Model 2; and systolic blood pressure (≤119, 120–139, 140–159, and ≥160 mm Hg) and serum total cholesterol (≤129, 130–199, 200–219, and ≥220 mg/dl) as dummy variables, and consumption of vegetable, fruit, fish and shellfish, meat and poultry, eggs, fat and oil, and salt as continuous variables, were further adjusted in Model 3. We defined Model 2 as the principal model and Model 3 as sensitivity analysis, because systolic blood pressure, serum total cholesterol, and food intake, which were adjusted in Model 3, may be intermediate factors. Thus, the possibility of overadjustment in Model 3 cannot be denied. All statistical analyses were performed using SPSS for Windows version 18.0J, SPSS, Tokyo, Japan. All values were 2-tailed, and $P < 0.05$ was considered to indicate statistical significance.

RESULTS

The analyzed participants were 9243 people (4045 men, and 5198 women), and their characteristics at baseline are shown in Table 1 by sex-specific tertile of milk and dairy product intake. There were significant differences among groups in milk and dairy product consumption, age, systolic blood pressure, serum total cholesterol, work category, total energy intake, and consumption of vegetables, fruit, meat and poultry, eggs, fat and oil, and salt (men and women); in history of diabetes and smoking status (men only); and in BMI, diastolic blood pressure, use of antihypertensives, and alcohol drinking habit (women only).

During the 24-year follow-up period, there were 2580 all-cause deaths (1372 men, 1208 women) and 893 CVD deaths (440 men, 453 women), of which 174 were CHD deaths (85 men, 89 women) and 417 were stroke deaths (217 men, 200 women).

The HRs for CVD death by tertile are shown in Table 2. For CVD death, the HR was marginally higher in the low consumption group in Model 2 among women (HR 1.27; 95% CI 0.99–1.58). The HR for CVD death significantly increased with decreasing milk and dairy product consumption in Model 2 among women (P for trend = 0.045). There was no significant association of milk and dairy product consumption with CVD death in men. For CHD death, the HR was marginally higher in the low consumption group in Model 2 among women (HR, 1.67; 95% CI, 0.99–2.80). The HRs for CHD death significantly increased with decreasing milk and dairy product consumption in all models (P for trend: Model 1, $P = 0.03$; Model 2; $P = 0.02$; Model 3, $P = 0.045$; data from Model 3 not shown). In men, there was no significant association of milk and dairy product consumption with CHD death. Milk and dairy product consumption was not significantly associated with stroke death in men or women.

The HRs for death from CVD, CHD, and stroke per 100-g/day increase in consumption of milk and dairy products are shown in Table 3. In Model 2, CVD death in women

Table 1. Baseline characteristics of participants by tertiles of milk and dairy product consumption (NIPPON DATA80, 1980)

Characteristic		Low	Moderate	High	*P* value	
					P^a	P^b
Men						
n		1349	1349	1347		
Range (g/d)		0–42.4	42.5–81.5	81.6–630.5		
Milk and dairy product consumption (g/d)		18.0 ± 15.0	61.5 ± 11.1	132.6 ± 53.3	<0.01	<0.01
Age (years)		52.1 ± 13.0	47.9 ± 12.5	50.8 ± 13.5	<0.01	
BMI (kg/m^2)		22.5 ± 2.8	22.5 ± 2.9	22.6 ± 2.9	0.35	0.09
Systolic blood pressure (mm Hg)		140.6 ± 21.7	136.6 ± 20.3	137.8 ± 20.2	<0.01	0.02
Diastolic blood pressure (mm Hg)		84.2 ± 12.6	83.1 ± 12.3	83.3 ± 12.0	0.06	0.31
Serum total cholesterol (mg/dl)		182.9 ± 32.9	186.2 ± 32.5	189.5 ± 32.8	<0.01	<0.01
History of diabetes (%)		3.9	3.3	5.4	0.02	
Use of antihypertensives (%)		10.1	8.2	10.7	0.07	
Smoking status	Never-smoker (%)	16.3	18.2	20.9	<0.01	
	≤20 cigarettes/day (%)	42.3	36.8	36.7		
	≥21 cigarettes/day (%)	24.3	27.9	22.2		
	Ex-smoker (%)	17.0	17.0	20.2		
Alcohol drinking habits	Never-drinker (%)	19.3	19.8	20.9	0.21	
	Occasional drinker (%)	24.2	27.7	27.5		
	Daily drinker (%)	51.1	47.4	46.3		
	Ex-drinker (%)	5.3	5.2	5.3		
Manager/professional (%)		41.1	50.3	51.4	<0.01	
Total energy intake (kcal/d)		2314 ± 489	2398 ± 460	2505 ± 464	<0.01	<0.01
Vegetable consumption (g/d)		284.8 ± 125.0	278.1 ± 101.7	299.0 ± 112.3	<0.01	<0.01
Fruit consumption (g/d)		121.7 ± 96.9	133.8 ± 86.9	168.7 ± 100.4	<0.01	<0.01
Fish and shellfish consumption (g/d)		124.8 ± 66.5	122.9 ± 63.0	127.5 ± 62.1	0.17	0.18
Meat and poultry consumption (g/d)		64.5 ± 41.3	73.8 ± 43.1	73.4 ± 39.8	<0.01	<0.01
Egg consumption (g/d)		37.1 ± 23.1	40.4 ± 20.6	44.3 ± 22.4	<0.01	<0.01
Fat and oil consumption (g/d)		14.7 ± 11.1	17.4 ± 11.1	18.9 ± 12.5	<0.01	<0.01
Salt consumption (g/d)		15.7 ± 6.2	14.7 ± 5.1	15.1 ± 5.2	<0.01	<0.01
Women						
n		1733	1734	1731		
Range (g/d)		0–53.6	53.7–105.6	105.7–577.5		
Milk and dairy product consumption (g/d)		22.7 ± 18.9	79.0 ± 14.8	168.3 ± 62.2	<0.01	<0.01
Age (years)		54.4 ± 13.1	49.0 ± 13.7	48.8 ± 12.4	<0.01	
BMI (kg/m^2)		23.1 ± 3.4	22.9 ± 3.4	22.6 ± 3.2	<0.01	<0.01
Systolic blood pressure (mm Hg)		138.0 ± 22.6	132.0 ± 20.6	131.6 ± 20.3	<0.01	<0.01
Diastolic blood pressure (mm Hg)		81.2 ± 12.2	78.6 ± 11.6	78.9 ± 11.6	<0.01	<0.01
Serum total cholesterol (mg/dl)		190.8 ± 33.6	187.1 ± 33.8	194.3 ± 34.6	<0.01	<0.01
History of diabetes (%)		1.5	2.2	2.6	0.07	
Use of antihypertensives (%)		14.5	9.4	10.0	<0.01	
Smoking status	Never-smoker (%)	87.9	89.1	90.2	0.37	
	≤20 cigarettes/day (%)	9.1	8.1	6.9		
	≥21 cigarettes/day (%)	0.6	0.7	0.8		
	Ex-smoker (%)	2.4	2.0	2.1		
Alcohol drinking habits	Never-drinker (%)	80.2	78.3	77.1	0.02	
	Occasional drinker (%)	14.8	18.0	18.7		
	Daily drinker (%)	3.3	2.7	2.5		
	Ex-drinker (%)	1.7	1.0	1.7		
Manager/professional (%)		8.7	13.4	13.9	<0.01	
Total energy intake (kcal/d)		1861 ± 408	1898 ± 362	2036 ± 376	<0.01	<0.01
Vegetable consumption (g/d)		269.1 ± 118.1	256.4 ± 94.8	280.1 ± 107.2	<0.01	<0.01
Fruit consumption (g/d)		165.0 ± 128.7	174.8 ± 111.1	222.1 ± 130.3	<0.01	<0.01
Fish and shellfish consumption (g/d)		98.7 ± 52.1	93.9 ± 44.9	96.3 ± 47.2	0.01	0.08
Meat and poultry consumption (g/d)		48.7 ± 37.5	54.0 ± 32.5	58.3 ± 31.8	<0.01	<0.01
Egg consumption (g/d)		31.5 ± 20.1	34.4 ± 18.1	38.5 ± 20.1	<0.01	<0.01
Fat and oil consumption (g/d)		13.0 ± 9.8	15.1 ± 9.4	17.9 ± 11.2	<0.01	<0.01
Salt consumption (g/d)		13.5 ± 5.3	12.6 ± 4.3	13.0 ± 4.5	<0.01	<0.01

[a]Tested by 1-way analysis of variance for continuous variables and by the chi-square test for categorical variables.
[b]Tested by analysis of covariance for continuous variables; adjusted for age.
Abbreviation: BMI, body mass index.

Table 2. Hazard ratios (95% CI) for mortality associated with milk and dairy product consumption (NIPPON DATA80, 1980–2004)

	Low	Moderate	High	*P* for trend
Men				
Person-years	26 861	28 419	27 100	
Cardiovascular disease				
Number of deaths	158	111	171	
Model 1[a]	0.90 (0.72–1.11)	0.89 (0.70–1.13)	1 (reference)	0.32
Model 2[b]	0.89 (0.72–1.11)	0.90 (0.71–1.15)	1 (reference)	0.31
Coronary heart disease				
Number of deaths	28	18	39	
Model 1[a]	0.69 (0.43–1.13)	0.59 (0.34–1.04)	1 (reference)	0.13
Model 2[b]	0.67 (0.41–1.11)	0.57 (0.32–1.01)	1 (reference)	0.11
Stroke				
Number of deaths	84	57	76	
Model 1[a]	1.07 (0.79–1.46)	1.04 (0.73–1.46)	1 (reference)	0.66
Model 2[b]	1.10 (0.80–1.50)	1.09 (0.77–1.54)	1 (reference)	0.58
Women				
Person-years	35 996	37 516	37 904	
Cardiovascular disease				
Number of deaths	215	127	111	
Model 1[a]	1.21 (0.96–1.52)	0.99 (0.77–1.28)	1 (reference)	0.07
Model 2[b]	1.27 (0.99–1.58)	1.03 (0.79–1.33)	1 (reference)	0.05
Coronary heart disease				
Number of deaths	51	17	21	
Model 1[a]	1.56 (0.94–2.60)	0.71 (0.37–1.35)	1 (reference)	0.03
Model 2[b]	1.67 (0.99–2.80)	0.72 (0.38–1.36)	1 (reference)	0.02
Stroke				
Number of deaths	98	54	48	
Model 1[a]	1.28 (0.91–1.82)	0.98 (0.66–1.45)	1 (reference)	0.12
Model 2[b]	1.34 (0.94–1.90)	1.04 (0.70–1.54)	1 (reference)	0.08

[a]Adjusted for age.
[b]Adjusted for age, body mass index, smoking status, alcohol drinking habit, history of diabetes, use of antihypertensives, work category, and total energy intake.

Table 3. Hazard ratios (95% CI) for mortality per 100-g/day increase in milk and dairy product consumption (NIPPON DATA80, 1980–2004)

	Model 1[a]	Model 2[b]
Men		
Cardiovascular disease	1.01 (0.88–1.17)	1.03 (0.89–1.20)
Coronary heart disease	1.24 (0.93–1.66)	1.33 (0.97–1.82)
Stroke	0.93 (0.75–1.14)	0.91 (0.74–1.13)
Women		
Cardiovascular disease	0.87 (0.76–1.01)	0.86 (0.74–0.99)
Coronary heart disease	0.76 (0.54–1.07)	0.73 (0.52–1.03)
Stroke	0.83 (0.67–1.03)	0.81 (0.65–1.01)

[a]Adjusted for age.
[b]Adjusted for age, body mass index, smoking status, alcohol drinking habit, history of diabetes, use of untihypertensives, work category, and total energy intake.

significantly decreased with each 100-g/day increase in milk and dairy product consumption (HR, 0.86; 95% CI, 0.74–0.99). The results were not materially different in women aged 50 years or older (data not shown).

DISCUSSION

A 24-year follow-up of Japanese participants showed that consumption of milk and dairy products was inversely associated with CVD death in women. No significant associations were observed in men.

An inverse association between dairy product consumption and CVD mortality was previously reported. Ness et al conducted a 25-year follow-up study of men in Scotland and found that milk consumption was inversely associated with death from all causes, CVD, and CHD.[4] In a cohort study of men, Elwood et al found that milk consumption was associated with lower levels of ischemic heart disease and stroke.[5] In a study of Australian adults who were followed for an average of 14.4 years, Bonthuis et al noted that full-fat dairy intake was inversely associated with CHD death.[3] In the Japan Collaborative Cohort study (JACC)[6] and the Japan Public Health Center study (JPHC),[7] calcium intake from dairy products was associated with lower stroke mortality in men and women, but no inverse association was seen for CHD death. Among these studies, the results from JACC and JPHC differ somewhat from the present results. In a systematic review of 10 cohort studies, however, Elwood et al suggested that milk drinking is associated with a small but meaningful reduction in vascular disease risk.[19]

In the present study, consumption of milk and dairy products was associated with CVD death only in women; no significant associations were seen in men. However, men consumed far less milk and dairy products than did women

in the present study. Furthermore, levels of milk and dairy product consumption in the present study were much lower than those reported in Western studies,[4,5] which observed an inverse association in men. For example, in the present study, daily consumption in the highest tertile of men was 81.6 g or more. In contrast, Ness et al reported[4] a daily consumption of 189 ml or less in the lowest tertile of participants. Had the men in the present study consumed much more milk and dairy products, the association of milk and dairy product consumption with mortality may have changed. Another reason for our findings in men is that men had a greater number of other risk factors, such as work stress, that may be more strongly related to CHD.[20] In the present study, although work category was adjusted for in the analysis, unidentified confounding factors may have remained.

Serum total cholesterol level was higher in the high intake group than in the lower intake groups. Serum cholesterol is a contributing factor for CVD,[21] and despite the high serum total cholesterol concentration in the high intake group, consumption of milk and dairy products was associated with lower CVD mortality in women. Model 3 further adjusted for serum total cholesterol, systolic blood pressure, and food intakes, which may be confounding factors or intermediate factors; however, the inverse association of milk and dairy product intake with CHD death was not substantially changed. This study began in 1980, and statin anticholesterol agents began to be marketed in Japan in 1989. Thus, statin use could be masking the effects of serum total cholesterol to some degree. In our previous cross-sectional study,[22] the regression coefficients between serum total cholesterol levels and milk and dairy products and other food groups were lower in the 1990s than in the 1980s.

We also found that blood pressure was lower in the high intake group than in the lower intake groups. Some studies have shown an inverse association between consumption of dairy products and blood pressure.[1,2,23,24] In a meta-analysis of randomized controlled trials, Van Mierlo et al suggested that calcium supplementation reduced blood pressure.[25] In an assessment of 2 cross-sectional studies (INTERMAP and INTERSALT), Kesteloot et al suggested that altered calcium homeostasis, as shown by increased calcium excretion, is associated with higher blood pressures.[26] In their meta-analysis of randomized controlled trials, Jia-Ying Xu et al showed that milk-derived tripeptides have hypotensive effects in prehypertensive and hypertensive adults.[27] Reports of an inverse association of milk and its ingredients with blood pressure are increasing; however, the association remains controversial.

It is unclear why there was an inverse association of milk and dairy product consumption with CVD death in the present study. Further research is warranted to elucidate the mechanisms involved. The same view was presented in the above-mentioned study showing an inverse association of CVD with milk and dairy products.[3] Moreover, although Elwood et al suggested that randomized controlled studies of dietary factors and disease risk would yield the best evidence, adequately powered randomized controlled trials of milk consumption would be impossible.[5] Two cohort studies[28,29] in Japan suggested that intakes of animal products such as eggs, dairy products, and fish were inversely associated with stroke risk. Among the present participants, those who consumed more milk also consumed more vegetables and fruits and moderate amounts of salt. To some extent, high milk and dairy product consumption may be an indicator of a healthy diet among Japanese.

The advantages of the present study were that it investigated a large, randomly selected sample of the general population of Japan, that it was a cohort study with 24 years of follow-up, that it was conducted in a region with low milk and dairy product consumption (in contrast to Western countries), and that milk and dairy product intake was based on weighed records, which is considered the gold standard for determining the weight of consumed foods.

The limitations of our study were that assessment of milk and dairy product intake at baseline may not have been representative of the full 24 years of the follow-up period. In addition, the calculated consumption at baseline may not have been the usual intake, because the food intake survey was based on records for only 3 days, excluding weekends and holidays.

Some studies analyzed food consumption by type of milk and dairy product, such as cheese and yogurt,[3,24] or by fat content.[1–3,24] The present analysis was done with milk and dairy products as a single group. However, daily consumption of milk and dairy products per person in 1980 was 115.2 g, with milk accounting for 107.2 g.[16] In recent years, the variety of milk and dairy products has increased, so future Japanese studies will likely analyze consumption by type of dairy product. Jenum et al reported that cardiovascular risk factors and population-level socioeconomic characteristics were strongly related to mortality.[30] Thus, future studies may need to analyze social background.

In conclusion, consumption of milk and dairy products (in the present research, almost entirely milk) was inversely associated with CVD death in women but not in men. Each 100-g/day increase in milk and dairy product consumption significantly decreased the HR for CVD death by 14%. No significant associations were observed in men. In Japan, milk and dairy product consumption has mainly been recommended for the purpose of increasing calcium intake but should be further investigated for its nutritional role in the Japanese diet.

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Conflicts of interest: None declared.

ONLINE ONLY MATERIALS

The Japanese-language abstract for articles can be accessed by clicking on the tab labeled Supplementary materials at the journal website http://dx.doi.org/10.2188/jea.JE20120054.

APPENDIX

The NIPPON DATA80/90 Research Group

Chairperson: Hirotsugu Ueshima (Department of Health Science, Shiga University of Medical Science, Otsu, Shiga).

Co-chairpersons: Akira Okayama (The First Institute for Health Promotion and Health Care, Japan Anti-Tuberculosis Association, Tokyo) for the NIPPON DATA80, and Tomonori Okamura (Department of Preventive Medicine and Public Health, Keio University, Tokyo) for the NIPPON DATA90.

Research members: Shigeyuki Saitoh (Department of Second Internal Medicine, Sapporo Medical University, Sapporo, Hokkaido), Kiyomi Sakata (Department of Hygiene and Preventive Medicine, Iwate Medical University, Morioka, Iwate), Atsushi Hozawa (Department of Preventive Medicine and Epidemiology, Tohoku Medical Megabank Organization, Tohoku University, Sendai, Miyagi), Takehito Hayakawa (Department of Hygiene and Preventive Medicine, Fukushima Medical University, Fukushima), Yosikazu Nakamura (Department of Public Health, Jichi Medical University, Shimotsuke, Tochigi), Yasuhiro Matsumura (Faculty of Health and Nutrition, Bunkyo University, Chigasaki, Kanagawa), Nobuo Nishi (Project for the National Health and Nutrition Survey, National Institute of Health and Nutrition, Tokyo), Nagako Okuda (Section of Shokuiku, Department of Nutritional Education, National Institute of Health and Nutrition, Tokyo), Fumiyoshi Kasagi (Institute of Radiation Epidemiology, Radiation Effects Association, Tokyo), Toru Izumi (Faculty of Medicine, Kitasato University, Sagamihara, Kanagawa), Toshiyuki Ojima (Department of Community Health and Preventive Medicine, Hamamatsu University School of Medicine, Hamamatsu, Shizuoka), Koji Tamakoshi (Department of Public Health and Health Information Dynamics, Nagoya University Graduate School of Medicine, Nagoya, Aichi), Hideaki Nakagawa (Department of Epidemiology and Public Health, Kanazawa Medical University, Kanazawa, Ishikawa), Katsuyuki Miura, Takayoshi Ohkubo, Yoshikuni Kita, Yasuyuki Nakamura (Cardiovascular Epidemiology, Kyoto Women's University, Kyoto), Katsushi Yoshita (Osaka City University Graduate School of Human Life Science, Osaka), Aya Kadota (Department of School Nursing and Health Education, Osaka Kyoiku University, Kashiwara, Osaka), Kazunori Kodama (Radiation Effects Research Foundation, Hiroshima) and Yutaka Kiyohara (Department of Environmental Medicine, Kyushu University, Fukuoka).

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(6)心電図上の早期再分極と冠動脈疾患死亡との関連：NIPPON DATA90 の 15 年追跡

研究協力者　久松　隆史　（滋賀医科大学呼吸循環器内科　大学院生）
研究分担者　大久保孝義　（滋賀医科大学社会医学講座公衆衛生学部門　准教授）
研究代表者　三浦　克之　（滋賀医科大学社会医学講座公衆衛生学部門　教授）
研究協力者　山本　孝　（滋賀医科大学呼吸循環器内科　講師）
研究協力者　藤吉　朗　（滋賀医科大学社会医学講座公衆衛生学部門　特任講師）
研究協力者　宮川　尚子　（滋賀医科大学社会医学講座公衆衛生学部門　大学院生）
研究分担者　門田　文　（大阪教育大学養護教育講座　准教授）
研究協力者　高嶋　直敬　（滋賀医科大学社会医学講座公衆衛生学部門　特任助教）
研究協力者　長澤　晋哉　（金沢医科大学公衆衛生学教室　助教）
研究分担者　喜多　義邦　（滋賀医科大学社会医学講座公衆衛生学部門　講師）
研究分担者　村上　義孝　（滋賀医科大学社会医学講座医療統計学部門　准教授）
研究分担者　岡山　明　（(公財)結核予防会第一健康相談所　所長）
研究協力者　堀江　稔　（滋賀医科大学呼吸循環器内科　教授）
研究分担者　岡村　智教　（慶應義塾大学医学部衛生学公衆衛生学　教授）
研究分担者　上島　弘嗣　（滋賀医科大学生活習慣病予防センター　特任教授）

【背景】早期再分極、心電図上 QRS-ST 接合部（J 点）の上昇は、最初に報告された 1936 年以降良性の心電図所見と考えられてきたが、近年になり心疾患死亡、心臓突然死との関連が報告されている。しかしながら、この早期再分極と各種の循環器疾患死亡（冠動脈疾患、心不全、不整脈、脳卒中、等）との関連について検討された報告は乏しい。

【方法】早期再分極、J 点の 0.1mV 以上の上昇、と各循環器疾患死亡との関連を検討するため、第 4 次循環器疾患基礎調査において無作為に抽出された日本全国 300 地区からの一般住民（年齢 30-95 歳）のうち、脳卒中や心筋梗塞の既往、ブルガダ型心電図、心室内伝導障害、等を有する者を除外した 7630 人（男性 3108 人、平均年齢 52.4 歳)を 1990 年から 2005 年まで 15 年間追跡した（NIPPON DATA90)。Cox 比例ハザードモデルを用いて、交絡因子を調整し、各循環器疾患死亡に対する早期再分極所見のハザード比を算出した。

【結果】心電図上の早期再分極は 264 人（3.5%）に認められた。早期再分極は、交絡因子を調整後も、心疾患死亡（調整後ハザード比 2.54; 95%信頼　区間 1.40-4.58; P = 0.002)、および冠動脈疾患死亡（調整後ハザード比 4.66; 95%信頼区間 2.30-9.46; P< 0.001）のリスク増加と関連していた。早期再分極と各循環器疾患死亡との関連は、

60 歳以上の群よりも 60 歳未満の群においてより強く認められた（年齢との交互作用のＰ値 ＜ 0.05)。

【結語】日本人の代表的抽出集団において、心電図上の早期再分極は心疾患死亡および冠動脈疾患死亡の独立した予測因子であった。特に 60 歳未満においてその関連が顕著であった。

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Association Between J-Point Elevation and Death From Coronary Heart Disease

– 15-Year Follow-up of the NIPPON DATA90 –

Takashi Hisamatsu, MD; Takayoshi Ohkubo, MD, PhD; Katsuyuki Miura, MD, PhD; Takashi Yamamoto, MD, PhD; Akira Fujiyoshi, MD, PhD; Naoko Miyagawa, BSc; Aya Kadota, MD, PhD; Naoyuki Takashima, MD, PhD; Shin-ya Nagasawa, MD, PhD; Yoshikuni Kita, PhD; Yoshitaka Murakami, PhD; Akira Okayama, MD, PhD; Minoru Horie, MD, PhD; Tomonori Okamura, MD, PhD; Hirotsugu Ueshima, MD, PhD for the NIPPON DATA90 Research Group

Background: An early repolarization pattern, characterized by an elevation of the QRS-ST junction (J-point) on 12-lead electrocardiography (ECG) is associated with cardiac and sudden death. However, little is known about the prognostic significance of J-point elevation for various disease-specific cardiovascular outcomes, including coronary heart disease (CHD).

Methods and Results: To investigate the association between the presence of J-point elevation ≥0.1 mV and various disease-specific cardiovascular outcomes, we conducted a 15-year prospective study in a representative general Japanese population of 7,630 individuals (41% men, mean age 52.4 years) who participated in the National Survey of Circulatory Disorders. Cox models were used to estimate the hazard ratios (HRs) adjusted for possible confounding factors. J-point elevation was present in 264 individuals (3.5%) and was associated with an increased risk of cardiac death (adjusted HR, 2.54; 95% confidence interval [CI] 1.40–4.58; P=0.002) and death from CHD (adjusted HR, 4.66; 95% CI 2.30–9.46; P<0.001). In a subgroup analysis by age, the association between J-point elevation and cardiovascular outcomes was more remarkable in middle-aged (<60 years) than in older individuals (≥60 years) (all P for interaction <0.05).

Conclusions: J-point elevation on standard 12-lead ECG was an independent predictor of cardiac death and death from CHD in a representative sample of the general Japanese population, particularly among the middle-aged.

Key Words: Cardiovascular diseases; Coronary heart disease; Electrocardiography; Epidemiology; J-point

Early repolarization, characterized by an elevation of the QRS-ST junction (ie, the J-point) on 12-lead electrocardiography (ECG), is a common finding,[1] and has been considered clinically benign since it was first reported in 1936.[2] However, recent prospective studies in the general population have demonstrated that J-point elevation is associated with an increased risk of cardiac[3,4] and sudden death.[5,6]

Following the publication of those studies, a number of reviews have speculated that several mechanisms underlie the association between J-point elevation and cardiac and arrhythmic death.[7–9] However, it remains controversial whether the J-point elevation is a manifestation of structural heart disease, such as coronary heart disease (CHD),[10–13] or primary electrical abnormalities.[14–16] Furthermore, little is known about the prognostic significance of a J-point elevation for various disease-specific cardiovascular outcomes, including CHD.

Therefore, a 15-year prospective study was conducted to investigate the long-term prognosis associated with J-point

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Department of Cardiovascular and Respiratory Medicine (T.H., T.Y., M.H.), Department of Health Science (T.H., T. Ohkubo, K.M., A.F., N.M., N.T., Y.K., H.U.), Department of Medical Statistics (Y.M.), Lifestyle-Related Disease Prevention Center (H.U.), Shiga University of Medical Science, Otsu; Department of School Nursing and Health Education, Osaka Kyoiku University, Osaka (A.K.); Department of Epidemiology and Public Health, Kanazawa Medical University, Kanazawa (S.N.); First Institute for Health Promotion and Health Care, Tokyo (A.O.); and Department of Preventive Medicine and Public Health, School of Medicine, Keio University, Tokyo (T. Okamura), Japan

Mailing address: Takashi Hisamatsu, MD, Department of Health Science, Shiga University of Medical Science, Setatsukinowa-cho, Otsu 520-2192, Japan. E-mail: hisataka@belle.shiga-med.ac.jp

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elevation in a representative sample of the general Japanese population aged 30 years or older who participated in the National Survey on Circulatory Disorders.

Methods

Study Design

Cohort studies of the National Survey on Circulatory Disorders and the National Nutrition Survey of Japan conducted in 1980 and 1990, respectively, by the Ministry of Health and Welfare are known as NIPPON DATA (National Integrated Project for Prospective Observation of Non-communicable Disease And its Trends in the Aged). We analyzed data from NIPPON DATA90 using the baseline survey conducted in 1990. The detailed methods are described elsewhere.[17–19] The present study was approved by the Institutional Review Board of Shiga University of Medical Science (No. 12-18, 2000; No. 17-21-1, 2010).

Study Participants

Members of an overall population (n=10,956) aged ≥30 years from 300 randomly selected health districts throughout Japan were invited to participate in the study. Among them, 8,383 community-based individuals agreed and the participation rate was 76.5% (8,383 of 10,956) before exclusion for the reasons indicated below. The survey consisted of a physical examination, blood test, self-administered questionnaire on lifestyle, dietary assessment, and standard 12-lead ECG recording. For the present study, participants were followed up to 2005 (NIPPON DATA90, 1990–2005).

A total of 753 participants were excluded from this analysis for the following reasons: previous myocardial infarction (MI) or stroke at baseline (n=247); major conduction defects on ECG (QRS duration ≥120 ms) or Brugada-type ECG[20,21] (n=172); and no ECG measurements at baseline (n=334). Thus, 7,630 individuals were included in the analysis (3,108 men; mean age 52.4 years, range 30–95 years).

Endpoint Determination

To determine the cause of death during the 15-year follow-up, the National Vital Statistics database of Japan was used with permission from the Management and Coordination Agency, Government of Japan. The underlying causes of death in the National Vital Statistics were coded according to the 9th International Classification of Disease (ICD9) until the end of 1994 and according to the 10th International Classification of Disease (ICD10) from 1995 onwards, as described elsewhere.[17,18]

The outcomes were cardiovascular death, cardiac death (ie, death from CHD, heart failure or arrhythmia) and death from stroke. The corresponding ICD9 and 10 codes were as follows: cardiovascular death, 393–459 (ICD9), I00–I99 (ICD10); cardiac death, 393–429 (ICD9), I01–I09, I11, I13, I20–I52 (ICD10); death from CHD including angina pectoris, acute MI, subsequent MI, complication following acute MI (within the 28-day period), other acute ischemic heart diseases, and chronic ischemic heart disease, 410–414 (ICD9), I20–I25 (ICD10); death from heart failure, 428 (ICD9), I50 (ICD10); death from arrhythmia, 426, 427, 798 (ICD9), I44–I49, R96, R98 (ICD10); and stroke death, 430–438 (ICD9), I60–I69 (ICD10).

Baseline Examination

A baseline survey was conducted at a local public health center in each area. Information on the history of cardiovascular disease, diabetes, medication usage, and smoking and drinking habits was obtained from a self-administered questionnaire and subsequently confirmed by public health nurses. Body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters. After a 5-min rest, blood pressure (BP) was measured by trained public health nurses using a standard mercury sphygmomanometer.

ECG measurements are described in more detail elsewhere.[17,22,23] In brief, standard 12-lead ECGs were recorded at baseline by trained technicians after the participant rested quietly supine for 5 min. ECG findings were independently evaluated by 2 trained researchers (blinded to outcome status) in each of 12 institutions in accordance with the Minnesota Code (MC), which was developed to document significant ECG patterns using objective comparison rules.[24] Codes that showed agreement between the two researchers' assessments were accepted; codes that showed disagreement were adjudicated by a panel of epidemiologists and cardiologists. J-point elevation was defined as an elevation of the QRS-ST junction (J-point) in at least one lead according to MC9.2 as follows: in the inferior (II, III, aV_F) and lateral leads (I, aV_L, V_6), an elevation of the J-point ≥0.1 mV from baseline; in the anterior leads (V_{1-5}), an elevation of the J-point ≥0.2 mV in leads V_{1-4} and ≥0.1 mV in lead V_5. Participants with major conduction defects on ECG (QRS duration ≥120 ms) were not included in this definition. ECG findings that we examined were also Q wave abnormality (MC1.1–1.3), left ventricular hypertrophy (LVH: MC3.1 or 3.3), major ST depression (MC4.1–4.3), major T abnormality (MC5.1 or 5.2).[24]

Non-fasting blood samples were obtained, and the serum was separated and centrifuged immediately after blood coagulation. Plasma samples were also obtained in a siliconized tube containing sodium fluoride. Serum total cholesterol was measured enzymatically. Lipid measurements were standardized using the Lipids Standardization Program from the Centers for Disease Control-National Heart, Lung and Blood Institute. Hemoglobin A_{1c} was determined by a latex cohesion method. All samples were shipped to a central laboratory (SRL, Tokyo, Japan) for measurements.

Statistical Analysis

Baseline characteristics of participants are presented as means and standard deviations for continuous variables and percentages for categorical variables. A comparison of baseline characteristics between each J-point elevation was made using statistical tests, such as the unpaired Student's t-test, Wilcoxon signed-rank test, and the chi-square test. Kaplan-Meier curves were plotted according to the presence or absence of J-point elevation, and differences between groups were examined by log-rank test. Cox proportional-hazard regression models were used to estimate the multivariate adjusted HRs of J-point elevation for mortality, as compared with an absence of J-point elevation. Model 1 was adjusted for age and sex; model 2 was adjusted for the same confounding factors as those used in a Finnish study[3] (ie, age, sex, BMI, smoking status, medication status, systolic BP, heart rate, LVH on ECG (classified according to MC3.1 or 3.3), and suspected CHD on ECG (classified according to MC1.1–1.3, 5.1–5.2, or 4.1–4.3); model 3 was adjusted for drinking habit, serum total cholesterol, and hemoglobin A1c in addition to the variables adjusted in Model 2. We also compared the prognostic significance of J-point elevation with other ECG risk markers such as suspected CHD and LVH.[3] A subgroup analysis was conducted according to age (<60 years, ≥60 years) on the basis of the Finnish study,[3] which examined parameters in subjects aged 30–59 years. Tests

Table 1. Baseline Characteristics of Study Participants in NIPPON DATA90

	No J-point elevation	J-point elevation	P value
n (%)	7,366 (96.5)	264 (3.5)	
Men	2,855 (38.8)	253 (95.8)	<0.001
Age, mean (SD), (years)	52.5 (13.7)	49.4 (12.6)	<0.001
Previous smoker	759 (10.3)	62 (23.5)	<0.001
Current smoker	2,012 (27.3)	142 (53.8)	<0.001
Alcohol drinker	1,949 (26.5)	167 (63.3)	<0.001
BMI, mean (SD), (kg/m²)	22.9 (3.2)	22.7 (2.7)	0.415
Serum TC, mean (SD), (mg/dl)	203.3 (37.9)	201.1 (35.8)	0.364
Hemoglobin A_{1c}, mean (SD), (%)	4.9 (0.7)	5.0 (0.9)	0.143
BP, mean (SD), (mmHg)			
Systolic	134.9 (20.5)	136.5 (20.8)	0.178
Diastolic	81.1 (11.8)	83.6 (13.4)	<0.001
Antihypertensive drug user	1,027 (13.9)	36 (13.6)	0.888
Bradycardia (heart rate ≤50 beats/min) on ECG	108 (1.5)	8 (3.0)	0.047
LVH on ECG*	755 (10.2)	86 (32.6)	<0.001
Suspected CHD on ECG†	334 (4.5)	13 (4.9)	0.765

Data are n (%) unless otherwise stated. *Diagnosis of LVH based on Minnesota Codes 3.1 or 3.3. †Suspicion of CHD based on Minnesota Codes 1.1–1.3, 5.1–5.2, or 4.1–4.3.
BMI, body mass index; TC, total cholesterol; BP, blood pressure; ECG, electrocardiography; CHD, coronary heart disease; LVH, left ventricular hypertrophy.

for interaction were performed by introducing a multiplicative interaction term into the main models. The statistical analyses were performed with SAS software, version 9.1.3 (SAS Institute, Cary, NC, USA). All probability values were 2-sided, and P<0.05 was considered significant.

Results

Baseline characteristics of the individuals with and without J-point elevation are presented in **Table 1**. Overall, a J-point elevation was present in 264 of 7,630 individuals (3.5%): in the anterior leads in 240 (3.1%) individuals, and in the inferior or lateral leads in 24 (0.3%) subjects. Individuals with J-point elevation were more often male, younger, smokers, alcohol drinkers, with higher diastolic BP, lower heart rate, and more likely to have a LVH on ECG than those without J-point elevation. Baseline characteristics of men with and without J-point elevation are also presented in **Table S1**: 95.8% of individuals with J-point elevation were men.

During the 15-year follow-up, 1,159 subjects died and of these, 325 died from cardiovascular causes. Among the cardiovascular deaths, 173 individuals died from cardiac causes, and 136 died from stroke. Among the cases of cardiac death, 71 subjects died from CHD (59 from acute MI, 83.1%), 66 died from heart failure, and only 12 died from arrhythmia.

Figure demonstrates the Kaplan-Meier analysis of individuals with and without J-point elevation. For those with J-point elevation, the death rate appeared to diverge from those without J-point elevation after 8 years of follow-up. There were no significant differences between the 2 groups in terms of cardiovascular death, though the difference tended to increase with time (**Figure A**). Individuals with J-point elevation had significantly higher rates of cardiac death and death from CHD than those without J-point elevation (**Figures B,C**).

Results of the multiple Cox proportional-hazard regression models are presented in **Table 2**. Individuals with J-point elevation had a significantly higher risk of cardiovascular death than those without J-point elevation in Model 1. In Models 2 and 3, statistical significance was lost, but the point estimate was only slightly lower than that in Model 1 (HR in Model 3=1.49; P=0.136). With respect to cardiac death and death from CHD, individuals with J-point elevation had a remarkably elevated risk compared with those without J-point elevation across each model (HRs in Model 3=2.54 for cardiac death, P=0.002; and 4.66 for death from CHD, P<0.001). We did not calculate HRs for death from heart failure, arrhythmia, and stroke owing to the small number of deaths: only 1 person died from each cause among the individuals with J-point elevation (**Table S2**). The results were similar when analyses were restricted to men (**Table S3**).

The comparative analysis of the prognostic value of ECG findings showed an increased risk for cardiac death among individuals with suspected CHD on ECG (adjusted HR=1.72; P=0.039) and among those with LVH on ECG (adjusted HR=1.48; P=0.042) (**Table 3**).

In the subgroup analysis by age, a more pronounced association between J-point elevation and cardiovascular outcomes was evident in middle-aged individuals (<60 years) compared with older individuals (≥60 years). The test for multiplicative interaction by age was significant for cardiovascular death (P for interaction <0.01), as well as for cardiac death and death from CHD (both Ps for interaction <0.05) (**Table 4**).

In the middle-aged group (<60 years), we further assessed the significance of J-point elevation according to the location of the leads. Compared with individuals without J-point elevation, the adjusted HRs for cardiovascular death, cardiac death, and death from CHD were significantly higher among those with J-point elevation in the inferior or lateral leads than in the anterior leads (**Table S4**). In addition, similar trends were observed in the prognostic value of J-point elevation among inferior and lateral leads (data not shown).

Discussion

The results of this 15-year prospective study of a representative sample of the general Japanese population suggest that

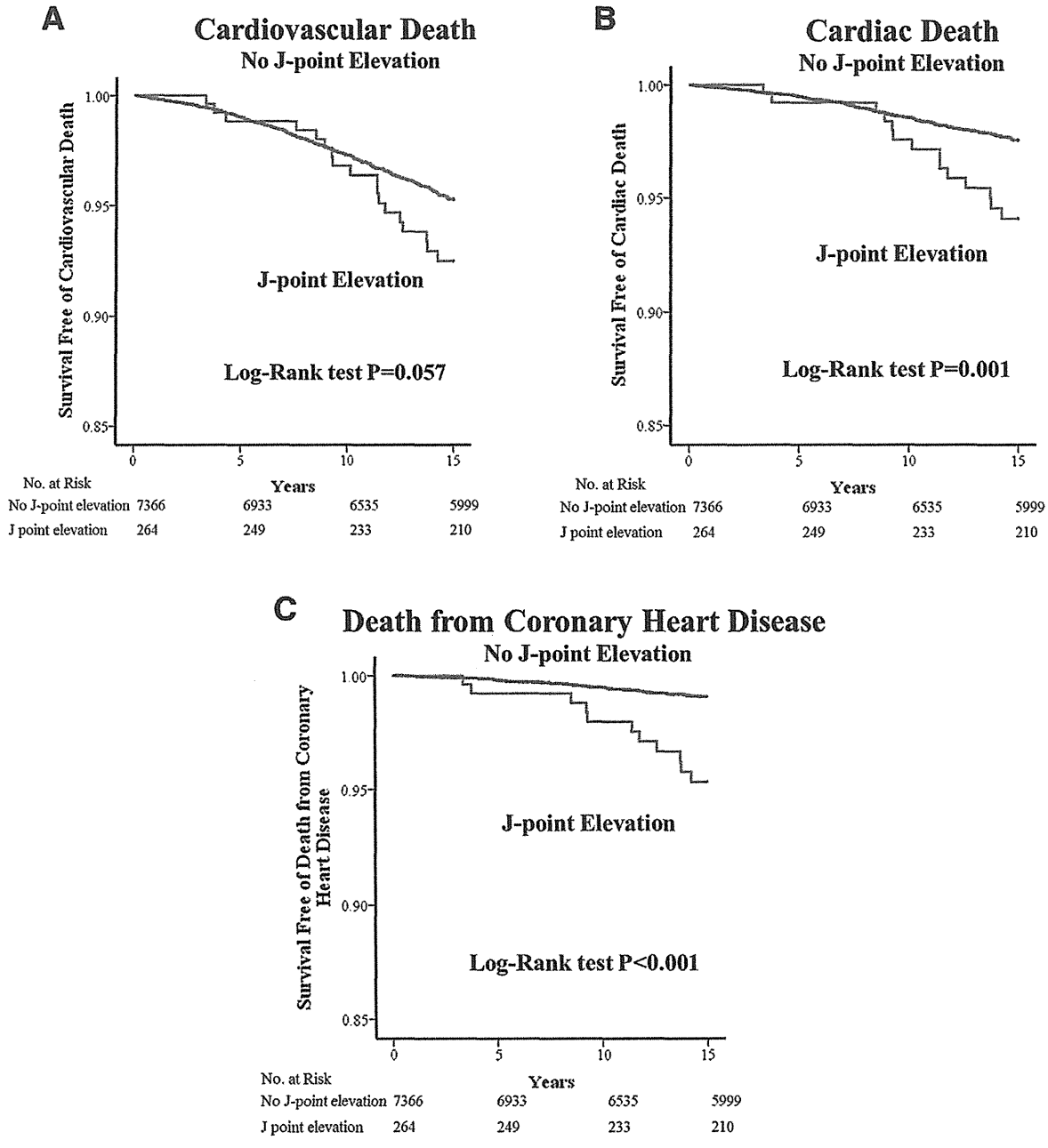

Figure. (A–C) Kaplan-Meier curves for cardiovascular outcomes according to the presence of J-point elevation in participants in NIPPON DATA90. Blue and red lines indicate individuals without and with J-point elevation, respectively. For those with J-point elevation, the death rate appears to diverge from those without J-point elevation after 8 years' follow-up.

J-point elevation on a standard 12-lead ECG is significantly associated with an increased risk of death from cardiac causes, particularly from CHD after adjustment for possible confounding factors. J-point elevation was a stronger predictor of death from cardiac causes and CHD than other ECG risk markers such as suspected CHD and LVH. Furthermore, the association was more apparent in middle-aged individuals. To our knowledge, this is the first community-based study to reveal a relationship between J-point elevation and death from CHD.

Comparison With Previous Studies

Our data are consistent with those from recent community-based studies.[3,4,6] In the present study, individuals with J-point elevation had a remarkably elevated risk of death from CHD. Conversely, recent studies in general Finnish, German, and US populations demonstrated that J-point elevation was associ-

Table 2. HRs of Cardiovascular Outcomes in 3,108 Men and 4,522 Women According to the Presence of a J-Point Elevation in a 15-Year Follow-up Study (NIPPON DATA90)

	No J-point elevation	J-point elevation	P value
Cardiovascular deaths			
n (%)	311 (4.2)	18 (6.8)	
Model 1 HR (95% CI)	1.00	1.86 (1.14–3.03)	0.013
Model 2 HR (95% CI)	1.00	1.55 (0.93–2.57)	0.092
Model 3 HR (95% CI)	1.00	1.49 (0.88–2.50)	0.136
Cardiac deaths			
n (%)	159 (2.2)	14 (5.3)	
Model 1 HR (95% CI)	1.00	2.79 (1.58–4.93)	<0.001
Model 2 HR (95% CI)	1.00	2.58 (1.43–4.65)	0.002
Model 3 HR (95% CI)	1.00	2.54 (1.40–4.58)	0.002
Deaths from CHD			
n (%)	60 (0.8)	11 (4.2)	
Model 1 HR (95% CI)	1.00	4.61 (2.35–9.04)	<0.001
Model 2 HR (95% CI)	1.00	4.74 (2.35–9.56)	<0.001
Model 3 HR (95% CI)	1.00	4.66 (2.30–9.46)	<0.001

Model 1 adjusted for age and sex. Model 2 adjusted for the same confounding factors used in a Finnish study:[3] age, sex, BMI, smoking status, medication status, systolic BP, heart rate, LVH on ECG (based on Minnesota Codes 3.1 or 3.3), and suspected CHD on ECG (based on Minnesota Codes 1.1–1.3, 5.1–5.2, or 4.1–4.3). Model 3 adjusted for drinking habits, serum TC, and hemoglobin A_{1c} in addition to the factors adjusted in Model 2.
HR, hazard ratio; CI, confidence interval. Other abbreviations as in Table 1.

Table 3. Comparative Analysis of the Prognostic Value of Electrocardiographic Findings in a 15-Year Follow-up Study (NIPPON DATA90)

	J-point elevation (n=264)		Suspected CHD (n=347)		LVH (n=841)	
	Adjusted HR (95% CI)	P value	Adjusted HR (95% CI)	P value	Adjusted HR (95% CI)	P value
Cardiovascular death	1.49 (0.88–2.50)	0.136	1.53 (1.05–2.25)	0.029	1.45 (1.09–1.92)	0.010
Cardiac death	2.54 (1.40–4.58)	0.002	1.72 (1.03–2.89)	0.039	1.48 (1.01–2.18)	0.042
Death from CHD	4.66 (2.30–9.46)	<0.001	1.57 (0.66–3.72)	0.304	1.34 (0.73–2.45)	0.353

HRs adjusted for age, sex, BMI, smoking status, medication status, systolic BP, drinking habit, serum TC, hemoglobin A_{1c}, heart rate, LVH on ECG (based on Minnesota Codes 3.1 or 3.3), and suspected CHD on ECG (based on Minnesota Codes 1.1–1.3, 5.1–5.2, or 4.1–4.3). Abbreviations as in Tables 1,2.

Table 4. Subgroup Analysis by Age: Multivariate Adjusted HRs for an Association of J-Point Elevation With Various Cardiovascular Outcomes in a 15-Year Follow-up Study (NIPPON DATA90)

	No. at risk	No. of J-point elevation	Cardiovascular deaths		Cardiac deaths		Deaths from CHD	
			No. of deaths	Adjusted HR* (95% CI)	No. of deaths	Adjusted HR* (95% CI)	No. of deaths	Adjusted HR* (95% CI)
<60 years	5,197	203	57	3.87 (1.85–8.10)†	36	5.26 (2.33–11.88)†	18	10.71 (3.75–30.57)†
≥60 years	2,433	61	272	0.79 (0.36–1.75)	137	1.46 (0.57–3.74)	53	2.66 (0.91–7.83)
P for interaction				0.003		0.010		0.048

*HRs adjusted for age, sex, BMI, smoking status, medication status, systolic BP, drinking habit, serum TC, hemoglobin A_{1c}, heart rate, LVH on ECG (based on Minnesota Codes 3.1 or 3.3), and suspected CHD on ECG (based on Minnesota Codes 1.1–1.3, 5.1–5.2, or 4.1–4.3). Significant differences in the HRs: †P<0.001. Abbreviations as in Tables 1,2.

ated with an increased risk of cardiac death, although the details of the cardiac death were not described.[3,4,6] However, other studies[25–27] and their national statistics reports found that CHD was the most common cause of cardiac death in each country, which suggests that J-point elevation may also have been associated with an increased risk of death from CHD in the Finnish, German, and US studies.

The present study found a significant association between J-point elevation and increased risk of death from cardiac causes, particularly from CHD, after multivariate adjustment, and it included such predictors of cardiovascular death as the classical risk factors and confounding ECG findings. However, in previous studies, although some risk factors were adjusted for in the multivariate analysis, other major risk factors, such as drinking habit, serum total cholesterol, and hemoglobin A_{1c} in the Finnish study[3] and confounding ECG findings in the German study,[4] were not adjusted. Furthermore, both classical risk factors and confounding ECG findings were not adjusted for in a recent Japanese study by Haruta et al,[5] which curiously reported that J-point elevation was associated with

decreased risk of cardiac death. Interestingly, in the present study, even after adjusting for all of the above factors, J-point elevation was still found to be an independent predictor of death from cardiac causes and CHD.

In the present study, J-point elevation, the definition of which according to MC9.2 is different from that used in other studies, was related to an increased risk of death from cardiac causes, particularly from CHD. Likewise, Olson et al used a similar definition to ours (including J-point elevation in the anterior leads and 1 lead affection) and reported that J-point elevation was significantly predictive of sudden cardiac death, primarily of the atherosclerotic type.[6] Our results also support ischemia-induced J-point elevation was observed in any lead of ECG.[28,29] Therefore, it may be reasonable to analyze the association of J-point elevation in any lead with cardiovascular outcomes, particularly CHD. In addition, consistent with previous studies,[3,4,30,31] J-point elevation in the inferior or lateral leads was a better predictor of increased risk of death from cardiovascular causes (including CHD) in the middle-aged group (<60 years).

Consistent with previous reports of 0.9–12.3% prevalence of J-point elevation,[1,6,32] the overall prevalence of J-point elevation in the present study was 3.5% (8.1% for males, 0.2% for females). These values are quite low compared with another Japanese population in which incident J-point elevation during the follow-up was found in 779 cases (13.0%) and prevalent J-point elevation in 650 cases (10.9%), resulting in a total prevalence of 23.9%.[5] Variation in estimates may be related to differences in trait definition, adjudication technique, and study sample demographics. For instance, the study describing the clinical correlates and heritability of J-point elevation in 2 large, population-based cohorts (Framingham Heart Study and Health 2000 Survey) demonstrated that participants in the Framingham Heart Study (mean age, ≈40 years) were approximately 10 years younger than those in the Health 2000 Survey cohort (mean age, ≈50 years) and the prevalence of J-point elevation was nearly twice as high (6.1% and 3.2%, respectively).[33] Therefore, the disparity in the prevalence of J-point elevation may result from differences between the Nagasaki study by Haruta et al and our study in the participants' ages. The population reported by Haruta et al was much younger (participants <40 years were 58.2%) compared with our study (21.9%). Interestingly, the mean ages of participants in our study (participants with and without J-point elevation: 49.4 and 52.5 years, respectively) were almost the same as those in the Health 2000 Survey and the prevalence of J-point elevation is very similar (3.5% and 3.2%, respectively).

Potential Mechanisms

The exact mechanisms for the association between J-point elevation and cardiovascular outcomes remain unclear. One possible interpretation for this association may be in the finding of several studies where J-point elevation on ECG represented a peri-infarction block,[12,13] which usually suggests latent CHD.[11] However, previous experimental studies have indicated that the mechanism for J-point elevation is related to fatal arrhythmia. Specifically, it was found that heterogeneity in ventricular repolarization manifests either as an early repolarization or J-point elevation on ECG, resulted in a vulnerability to ventricular arrhythmia.[14–16] Accordingly, it is possible that J-point elevation may derive from either structural heart disease, such as CHD, or primary electrical abnormalities, both of which produce vulnerability to serious ventricular arrhythmia and sudden death.[10–13] However, the Japanese population has a very low rate of sudden death compared with Western populations.[34] Thus, in the present study, we did not observe a sufficient number of arrhythmic deaths, as opposed to the significant association between J-point elevation and death from CHD. Further studies are required to clarify the potential mechanisms underlying the association between J-point elevation and cardiovascular outcomes, as well as the difference in the prognostic value for death from CHD between J-point elevation and suspected CHD on ECG.

Study Limitations

First, the number of deaths was too small to comprehensively analyze the prognostic significance of arrhythmia associated with J-point elevation. During the 15-year follow-up, we observed a lower prevalence of J-point elevation and mortality than that found by recent community-based studies.[3–6] We calculated a wide range of HRs of J-point elevation, particularly in the inferior or lateral leads. Second, we did not have any incidence data, and as a result we could not examine whether there were any differences between incidence and mortality. Third, the use of death certificate data may lead to misclassification in the cause of death. It was reported that most cases of sudden cardiac death from arrhythmia tend to be described as CHD or heart failure on Japanese death certificates.[35] Fourth, uncertainty around the cause of death from CHD, other than acute MI, may limit the present results. Lastly, we did not have detailed information on the amplitude or morphology of the J-point elevation (eg, notching or slurring, and horizontal/descending or rapidly ascending/upsloping in the ST segment). A rapidly ascending ST segment after J-point elevation appears to be a benign variant of early repolarization.[36]

Conclusions

We demonstrated that J-point elevation on standard 12-lead ECG is an independent predictor of death from cardiac causes, particularly from CHD, in a representative sample of the general Japanese population. J-point elevation may be a useful marker for cardiac and CHD risk stratification. Future studies are necessary to disclose the potential mechanisms responsible for this association.

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The authors are deeply grateful to all the staff members of the NIPPON DATA80/90 Research Group, who are listed in the **Appendix (Data S1)**.

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Supplementary Files

Supplementary File 1

Table S1. Baseline Characteristics of the Men in NIPPON DATA90

Table S2. Number of Deaths Among 3,108 Men and 4,522 Women According to the Presence of a J-Point Elevation in a 15-Year Follow-up Study (NIPPON DATA90)

Table S3. HRs of Cardiovascular Outcomes in 3,108 Men According to the Presence of a J-Point Elevation in a 15-Year Follow-up Study (NIPPON DATA90)

Table S4. Subgroup Analysis of the Middle-Aged Group (<60 Years) According to the Location of the J-Point Elevation in a 15-Year Follow-up Study (NIPPON DATA90)

Data S1. Appendix

Please find supplementary file(s);
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Supplementary File

Association Between J-Point Elevation and Death From Coronary Heart Disease

– 15-Year Follow-up of the NIPPON DATA90 –

Takashi Hisamatsu, MD; Takayoshi Ohkubo, MD, PhD; Katsuyuki Miura, MD, PhD; Takashi Yamamoto, MD, PhD; Akira Fujiyoshi, MD, PhD; Naoko Miyagawa, BSc; Aya Kadota, MD, PhD; Naoyuki Takashima, MD, PhD; Shin-ya Nagasawa, MD, PhD; Yoshikuni Kita, PhD; Yoshitaka Murakami, PhD; Akira Okayama, MD, PhD; Minoru Horie, MD, PhD; Tomonori Okamura, MD, PhD; Hirotsugu Ueshima, MD, PhD for the NIPPON DATA90 Research Group

Supplementary File 1

Table S1. Baseline Characteristics of the Men in NIPPON DATA90

	No J-point elevation	J-point elevation	P value
n (%)	2,855 (91.9)	253 (8.1)	
Age, mean (SD), (years)	52.8 (13.5)	49.1 (12.2)	<0.001
Previous smoker	645 (22.6)	62 (24.5)	0.486
Current smoker	1,593 (55.8)	141 (55.7)	0.984
Alcohol drinker	1,652 (57.9)	167 (66.0)	0.012
BMI, mean (SD), (kg/m^2)	23.0 (3.1)	22.8 (2.7)	0.143
Serum TC, mean (SD), (mg/dl)	198.4 (36.5)	200.6 (35.5)	0.331
Hemoglobin A_{1c}, mean (SD), (%)	5.0 (0.7)	5.0 (0.9)	0.319
BP, mean (SD), (mmHg)			
Systolic	137.5 (19.9)	136.0 (20.3)	0.358
Diastolic	83.7 (11.4)	83.6 (13.3)	0.846
Antihypertensive drug user	347 (12.2)	32 (12.6)	0.818
Bradycardia (heart rate ≤50 beats/min) on ECG	67 (2.3)	8 (3.2)	0.418
LVH on ECG*	473 (16.6)	79 (31.2)	<0.001
Suspected CHD on ECG†	121 (4.2)	10 (4.0)	0.828

Data are n (%) unless otherwise stated. *Diagnosis of LVH based on Minnesota Codes 3.1 or 3.3. †Suspicion of CHD based on Minnesota Codes 1.1–1.3, 5.1–5.2, or 4.1–4.3.
BMI, body mass index; TC, total cholesterol; BP, blood pressure; ECG, electrocardiography; CHD, coronary heart disease; LVH, left ventricular hypertrophy.

Table S2. Number of Deaths Among 3,108 Men and 4,522 Women According to the Presence of a J-Point Elevation in a 15-Year Follow-up Study (NIPPON DATA90)

	No J-point elevation, n (%)	J-point elevation, n (%)
Death from heart failure	65 (0.9)	1 (0.4)
Death from arrhythmia	11 (0.1)	1 (0.4)
Stroke death	135 (1.8)	1 (0.4)

Table S3. HRs of Cardiovascular Outcomes in 3,108 Men According to the Presence of a J-Point Elevation in a 15-Year Follow-up Study (NIPPON DATA90)

	No J-point elevation	J-point elevation	P value
Cardiovascular deaths			
n (%)	144 (5.0)	17 (6.7)	
Model 1 HR (95% CI)	1.00	1.83 (1.11–3.02)	0.019
Model 2 HR (95% CI)	1.00	1.64 (0.96–2.78)	0.069
Model 3 HR (95% CI)	1.00	1.53 (0.89–2.63)	0.127
Cardiac deaths			
n (%)	74 (2.6)	13 (5.1)	
Model 1 HR (95% CI)	1.00	2.64 (1.47–4.77)	0.001
Model 2 HR (95% CI)	1.00	2.62 (1.42–4.84)	0.002
Model 3 HR (95% CI)	1.00	2.55 (1.37–4.75)	0.003
Deaths from CHD			
n (%)	36 (1.3)	10 (4.0)	
Model 1 HR (95% CI)	1.00	4.08 (2.02–8.24)	<0.001
Model 2 HR (95% CI)	1.00	4.48 (2.14–9.37)	<0.001
Model 3 HR (95% CI)	1.00	4.34 (2.05–9.18)	<0.001

Model 1 adjusted for age. Model 2 adjusted for the same confounding factors used in a Finnish study*: age, BMI, smoking status, medication status, systolic BP, heart rate, LVH on ECG (based on Minnesota Codes 3.1 or 3.3), and suspected CHD on ECG (based on Minnesota Codes 1.1–1.3, 5.1–5.2, or 4.1–4.3). Model 3 adjusted for drinking habits, serum TC, and hemoglobin A_{1c} in addition to the factors adjusted in Model 2.
CI, confidence interval; HR, hazard ratio. Other abbreviation as in Table S1.
*Tikkanen JT, Anttonen O, Junttila MJ, Aro AL, Kerola T, Rissanen HA, et al. Long-term outcome associated with early repolarization on electrocardiography. *N Engl J Med* 2009; **361:** 2529–2537.

Table S4. Subgroup Analysis of the Middle-Aged Group (<60 Years) According to the Location of the J-Point Elevation in a 15-Year Follow-up Study (NIPPON DATA90)

	No J-point elevation (n=4,994)		J-point elevation					
			Anterior leads (n=186)			Inferior or lateral leads (n=17)		
	No. of deaths	HR	No. of deaths	Adjusted HR* (95% CI)	P value	No. of deaths	Adjusted HR* (95% CI)	P value
Cardiovascular deaths	47	1.00	7	2.89 (1.24–6.71)	0.014	3	16.83 (4.85–58.32)	<0.001
Cardiac deaths	27	1.00	6	3.68 (1.44–9.41)	0.007	3	33.95 (9.30–123.96)	<0.001
Deaths from CHD	11	1.00	5	7.97 (2.50–25.42)	<0.001	2	54.27 (10.23–288.01)	<0.001

*HRs adjusted for age, sex, BMI, smoking status, medication status, systolic BP, drinking habits, serum TC, hemoglobin A_{1c}, heart rate, LVH on ECG (based on Minnesota Codes 3.1 or 3.3), and suspected CHD on ECG (based on Minnesota Codes 1.1–1.3, 5.1–5.2, or 4.1–4.3). Other abbreviations as in Tables 1,3.

Data S1. Appendix

The NIPPON DATA80/90 Research Group

Research members: Shigeyuki Saitoh (Sapporo Medical University School of Health Science, Sapporo), Kiyomi Sakata (Department of Hygiene and Preventive Medicine, Iwate Medical University, Morioka), Atsushi Hozawa (Department of Preventive Medicine and Epidemiology, Tohoku Medical Megabank Organization, Tohoku University, Sendai), Takehito Hayakawa (Department of Hygiene and Preventive Medicine, Fukushima Medical University, Fukushima), Yosikazu Nakamura (Department of Public Health, Jichi Medical University, Shimotsuke), Yasuhiro Matsumura (Faculty of Health and Nutrition, Bunkyo University, Chigasaki), Nobuo Nishi (Project for the National Health and Nutrition Survey, National Institute of Health and Nutrition, Tokyo), Nagako Okuda (Department of Nutrition Epidemiology, National Institute of Health and Nutrition, Tokyo), Fumiyoshi Kasagi (Institute of Radiation Epidemiology, Radiation Effects Association, Tokyo), Toru Izumi (Faculty of Medicine, Kitasato University, Sagamihara), Toshiyuki Ojima (Department of Community Health and Preventive Medicine, Hamamatsu University School of Medicine, Hamamatsu), Koji Tamakoshi (Department of Public Health and Health Information Dynamics, Nagoya University Graduate School of Medicine, Nagoya), Hideaki Nakagawa (Department of Epidemiology and Public Health, Kanazawa Medical University, Kanazawa), Katsuyuki Miura, Takayoshi Ohkubo, Yoshikuni Kita (Department of Health Science, Shiga University of Medical Science, Otsu), Yasuyuki Nakamura (Cardiovascular Epidemiology, Kyoto Women's University, Kyoto), Katsushi Yoshita (Osaka City University Graduate School of human life science, Osaka), Aya Kadota (Department of School Nursing and Health Education, Osaka Kyoiku University, Kashiwara, Osaka), Kazunori Kodama (Radiation Effects Research Foundation, Hiroshima) and Yutaka Kiyohara (Department of Environmental Medicine, Kyushu University, Fukuoka).