Association between consumption of small fish and all-cause mortality among Japanese: the Japan Multi-Institutional Collaborative Cohort Study

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Short running head: Intake of small fish and all-cause mortality

Conflict of Interest:

All authors declare no conflicts of interest.

ABSTRACT

Objective: Although small fish are an important source of micronutrients, the relationship between their intake and mortality remains unclear. This study aimed to clarify the association between intake of small fish and all-cause and cause-specific mortality.

Design: We used the data from a cohort study in Japan. The frequency of the intake of small fish was assessed using a validated food frequency questionnaire. The hazard ratios (HRs) and 95% confidence intervals (CIs) for all-cause and cause-specific mortality according to the frequency of the intake of small fish by sex were estimated using a Cox proportional hazard model with adjustments for covariates.

Setting: The Japan Multi-Institutional Collaborative Cohort (J-MICC) Study.

Participants: A total of 80,802 participants (34,555 males and 46,247 females), aged 35–69 years.

Results: During a mean follow-up of 9.0 years, we identified 2,482 deaths including 1,495 cancer-related deaths. The intake of small fish was statistically significantly and inversely associated with the risk of all-cause and cancer mortality in females. The multivariable-adjusted HRs (95% CIs) in females for all-cause mortality according to the intake were 0.68 (0.55–0.85) for intakes 1–3 times/month, 0.72 (0.57–0.90) for 1–2 times/week, and 0.69 (0.54–0.88) for ≥3 times/week, compared with the rare intake. The corresponding HRs (95% CIs) in females for cancer mortality were 0.72 (0.54–0.96), 0.71 (0.53–0.96), and 0.64 (0.46–0.89), respectively. No statistically significant association was observed in males.

Conclusions: Intake of small fish may reduce the risk of all-cause and cancer mortality in Japanese females.

Keywords: small fish, all-cause mortality, cancer, cohort studies, Japanese

Introduction

Small fish are among the important sources of micronutrients such as calcium, magnesium, and vitamins A and D, when consumed whole with bones and inner organs [1-6]. These nutrients contribute to the prevention of non-communicable diseases, including cardiovascular disease (CVD) and cancer, through their antihypertensive, atherosclerosis-inhibiting, and antitumor effects [7-12]. Bone, eyes, and inner organs of fish are reservoirs of most micronutrients, including calcium and vitamin A [1, 2]. Unlike large fish in which bones and organs are often discarded, small fish offer a unique advantage in that they can be consumed as a whole.

Japanese people habitually eat several types of small fish, including whitebait, Atlantic capelin [shishamo], Japanese smelt (Hypomesus nipponensis) [wakasagi], small horse mackerel, young sweetfish, and small dried sardine, as a whole. These small fish are consumed in a variety of ways, such as raw or marinated in vinegar, simmered in soy sauce, salted semi-dried, and deep fried. Fish, such as capelin and smelt are mostly 10–15 cm in length, whereas smaller ones, such as whitebait, are less than 3.5 cm in length[13]. These small fish are retailed as frozen or refrigerated products throughout the year. The habit of eating small fish as a whole is also found in other Asian countries besides Japan and some African and European countries. In developing countries, intake of affordable small fish as a whole is expected to improve severe micronutrient deficiency [1-3, 14].

Fish intake has been suggested to be associated with a lower risk of all-cause, cancer, and CVD mortality in several cohort studies and meta-analyses, with inconsistent findings for cancer mortality [15-20]. Such association, however, has not been specifically assessed for the intake of small fish. Considering that intake of small fish as a whole including bone and organs may be effective in reducing the mortality risk in a manner different from the ones for non-small fish, it is necessary to assess the association between mortality and the intake of small fish instead of fish consumption in general.

To address this issue, in the present study, we aimed at elucidating the association between the intake of small fish and the risk of all-cause, cancer, and CVD mortality using data from a large-scale cohort study in Japan.

Methods

Participants

For the present analysis, participants, aged 35–69 years, in the Japan Multi-Institutional Collaborative Cohort (J-MICC) Study were included. The details of the J-MICC Study and the recruitment of participants were described previously [21]. In brief, the J-MICC Study is a large cohort study in Japan, which was launched in 2005 and enrolled residents in the community, health check examinees, and first-visit patients at a cancer hospital. Some participants were recruited in 2004. The baseline survey included 92,529 adults from 14 study areas (the dataset used in the present study was completed after cleaning the collected data on June 1, 2021). The sample size was determined considering the feasibility including budgets and statistical power for the incidence of major cancer types, which was the primary outcome of the J-MICC Study. **Figure 1** shows the flowchart for selection of participants for the analysis. Participants without a follow-up, those with a self-reported medical history of any cancer, stroke, myocardial infarction, and angina pectoris, and those who died within a year from the baseline were excluded. Furthermore, we excluded participants with missing data for the intake of small fish and those who deviated from the sex-specific mean $\pm$ 3 SD for total energy intake. Thus, 80,802 individuals (34,555 males and 46,247 females) were finally included in the present study.

Assessment of lifestyle factors and dietary intake

The height and weight of participants were measured directly on the day of the survey in 12 areas and were self-reported by participants in 2 areas. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters (kg/m^2). Lifestyle factors, including smoking habit, alcohol consumption, education level, leisure-time physical activity, medical history, age at menarche, number of births, and menopausal status were assessed using a self-administered questionnaire at baseline. For smoking habit, participants reported whether they were current smokers, had quit smoking, or never smoked. Participants who reported smoking indicated the average number of cigarettes per day, and those who reported quitting indicated how many years (or months) ago they quit. Ethanol intake (g/day) was estimated for current drinkers (defined as those who consumed alcohol at least once a month during the last year) based on the reported consumption frequency and amount consumed each time for six alcoholic beverages (Japanese *sake*, *shochu*, *shochu*-based cocktails, beer, whisky, and wine) [22]. For education level, participants reported the last school level they graduated from

(excluding dropout) from one of the following seven categories: elementary school or junior high school, high school, vocational school, junior college or technical school, college or university, graduate school, and others. Participants from three study areas were not asked about their education level and were assigned to an additional category for missing data. Leisure-time physical activity was estimated based on the frequency and duration of leisure-time activities [23]. Leisure-time physical activity was calculated as metabolic equivalent hours per day (MET·hours/day) by multiplying the assigned daily mean frequency, mean duration (time in hours), and MET value together for each activity: low-intensity physical activity (e.g., walking and golf, assigned 3.4 METs), moderate-intensity physical activity (e.g., jogging and swimming, 7.0 METs), and high-intensity physical activity (e.g., marathon running and martial arts, 10 METs). The frequency (assigned as daily mean frequency) was reported in five categories as follows: none (0), 1–3 times/month (2/30), 1–2 times/week (1.5/7), 3–4 times/week (3.5/7), and ≥5 times/week (6/7). The mean duration (assigned as time in hours) was reported in six categories as follows: <30 minutes (15/60), 30 minutes to <1 hour (45/60), 1 to <2 hours (1.5), 2 to <3 hours (2.5), 3 to <4 hours (3.5), and ≥4 hours (4.0). The questionnaire was based on a similar validated survey used in the Japan Public Health Center-based Prospective Study [24]. Patient medical history was self-reported, and the past and present history were considered a positive history. Age at menarche, number of births, and menopausal status were also self-reported.

The average daily intake of energy, selected foods/food groups (green and yellow vegetables, light-colored vegetables, fruit, meat, and rice), and nutrients (sodium, dietary fiber, n-3 highly unsaturated fatty acids [n-3 HUFAs, including eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and docosapentaenoic acid], calcium, vitamin D, retinol, and carotene) were estimated using a validated short food frequency questionnaire (FFQ), including 47 foods and beverages, based on the Standard Tables of Food Composition in Japan, the fifth revised edition at baseline [25-28]. Retinol intake was estimated as retinol equivalents, and carotene intake was estimated as β-carotene equivalents [28]. Only the baseline FFQ results were considered. Nutrient intakes from supplements were not included. The FFQ included seven questions that assessed the intake of fish (raw fish, grilled fish, and boiled fish), small fish (Atlantic capelin and dried young sardines [whitebait]), canned tuna, crustacean and mollusks (shrimp, crab, octopus, and squid), shellfish (clams and oysters), roe (salted cod roe and salmon roe), and fish-paste products (baked bar [chikuwa] and steamed cake [kamaboko]) with eight possible responses on intake frequency (rarely, 1–3 times/month, 1–2 times/week, 3–4

times/week, 5–6 times/week, 1 time/day, 2 times/day, and ≥3 times/day). The items listed in parentheses in the FFQ are examples of questions preceding the parentheses. Atlantic capelin and dried young sardines [whitebait] were listed as examples of small fish in the parentheses. We evaluated the validity of intake of small fish estimated using the FFQs by comparing the estimate with the intake based on 12-day dietary records. Both the intakes were $\log_e$-transformed. The Pearson correlation coefficients (de-attenuated for intra-individual variation) between the FFQ and dietary records were 0.48 for men and 0.51 for women [27]. We adjusted for total energy from intake of foods and nutrients using the density method [29]. We then divided the subjects into sex-specific quartiles according to energy-adjusted intake of each food or nutrient. To validate the consumption of other foods as an adjusted covariate, the Spearman's correlation coefficients (de-attenuated for intra-individual variation and energy-adjusted) between the FFQ and dietary records were calculated and determined to be 0.34 in males and 0.36 in females for green and yellow vegetables, 0.35 in males and 0.24 in females for light-colored vegetables, 0.62 in males and 0.58 in females for fruit, 0.41 in males and 0.41 in females for meat, and 0.67 in males and 0.61 in females for rice [27].

Regarding total energy and nutrient intake adjusted as covariates, the Pearson's correlation coefficients (de-attenuated for intra-individual variation, $\log_e$-transformed, and energy-adjusted) between the FFQ and dietary records were determined as 0.49 in males and 0.44 in females for total energy, 0.24 in males and 0.35 in females for sodium, 0.36 in males and 0.47 in females for dietary fiber, 0.36 in males and 0.35 in females for n-3 HUFAs, 0.49 in males and 0.59 in females for calcium, 0.65 in males and 0.40 in females for vitamin D, 0.27 in males and 0.22 in females for retinol, and 0.39 in males and 0.38 in females for carotene [26].

We calculated the Japanese diet index (JDI) to examine whether the intake of small fish is associated with mortality risk, independently of the degree of adherence to the Japanese diet. This is because the Japanese diet is reported to be associated with a lower risk of mortality [30, 31]. The original JDI consists of the following eight components: rice, miso soup, seaweeds, pickles, green and yellow vegetables, fish, green tea, and beef and pork. We used only seven factors, excluding pickles, for the JDI because of no information on pickles. Pickles are important sodium sources in the Japanese diet, so they are sometimes incorporated in an FFQ to estimate sodium intake. In the development of the FFQ used in our study, however, pickles were not included because sodium intake was not an original target nutrient. The method to estimate sodium intake was devised after FFQ development. Since the FFQ is reasonably valid for small fish intake, it was appropriate for the present study hypothesis. The fish component of

the JDI was calculated using the total consumption of fish and shellfish, including small fish. The beef and pork represent non-adherence to the Japanese diet, and participants received one point if their intake (g/day) was less than the sex-specific median for the entire population of this study. The remaining six components represent adherence to the Japanese diet; participants received one point if the intake (g/day) was more than or equal to the sex-specific median for the entire population of this study. The intakes of seven components for participants with missing data for the intake were considered zero. The JDI score ranged from 0 to 7, with higher scores indicating greater conformity to the Japanese diet.

Follow-up and endpoint

We followed eligible participants from the enrollment date (from February 11, 2004, to March 31, 2014) to December 31, 2017 in 11 study areas (Chiba, Aichi Cancer Center, Okazaki, Shizuoka, Takashima, Kyoto, Fukuoka, Saga, Kagoshima, Tokushima, and Shizuoka-Sakuragaoka), or to December 31, 2018 in 3 ones (Kyushu and Okinawa Population Study [KOPS], Iga, and Daiko). Information on residence and survival status was obtained from the resident registers annually or biennially. During the follow-up period, 4,400 participants (5.4%) were moved out of the study areas and 165 participants (0.2%) were unable to follow up because of other reasons. They were censored at the last date when they were known to reside in the study areas. The causes of death were identified based on the abstracts of death certificates provided by the Japanese Ministry of Health, Labour and Welfare and were coded according to the International Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10). The primary outcome of this study was death of all causes, and the secondary outcomes were death of cancer (ICD-10: C00–C97), CVD including heart disease and cerebrovascular disease (ICD-10: I00–I99), and other causes (non-cancer, non-CVD).

Statistical analysis

Participants were classified into four groups according to the frequency of the intake of small fish by sex, as follows: rarely, 1–3 times/month, 1–2 times/week, and ≥3 times/week. Differences in the means of age and leisure-time physical activity between the frequency categories were tested using one-way ANOVA. Differences in the median of energy-adjusted intakes of small fish and non-small fish (raw fish, grilled fish, and boiled fish; do not include other seafood items) between the frequency categories were analyzed using Kruskal-Wallis test. Differences in the proportions of categorical variables between the frequency groups were

tested using the chi-squared test. Because a considerable proportion of participants (40.8%) filled out the FFQ and questionnaire for lifestyle factors only at baseline, only baseline responses to the FFQ and questionnaire were considered, as these were provided by all the participants.

The sex-specific hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) for all-cause, cancer, CVD, and other-cause mortality according to the frequency of the intake of small fish were estimated using the Cox proportional hazards model with adjustments for potential confounding factors. The end of follow-up was defined as the date of death, date of moving out of the study area, or the end of follow-up, whichever occurred first. The lowest category of the intake of small fish (rarely) was considered the reference group. The categories were determined so that each category has enough number of participants. The linear trends for the risk were evaluated using an ordinal number assigned to the frequency categories (rarely: 1; 1–3 times/month: 2; 1–2 times/week: 3; and ≥3 times/week: 4).

Four multivariable models were established as follows: Model 1: adjusted for age at baseline (as a continuous variable) and study areas (Chiba, Aichi Cancer Center, Okazaki, Shizuoka, Iga, Daiko, Takashima, Kyoto, Fukuoka, Saga, Kagoshima, Tokushima, Kyushu and Okinawa Population Study [KOPS], Shizuoka-Sakuragaoka). Model 2: adjusted for covariates in Model 1 plus BMI (<18.5, 18.5 to <25, ≥25 kg/m^2), smoking habit (for males: never, former [quit smoking ≥10, 5 to <10, <5 years ago], current [<20, 20 to <40, ≥40 cigarettes/day], and for females: never, former [quit smoking ≥10, <10 years ago], current [<20, ≥20 cigarettes/day]), alcohol consumption (for males: never, former, current [<23, 23 to <46, ≥46 g/day ethanol]; and for females: never, former, current [<23, ≥23 g/day ethanol]; 23 g/day ethanol is equivalent to 180 mL of Japanese *sake*), education level (junior high school or under [≤9 years], high school [10–12 years], junior college or vocational school [13–15 years], and college, university or above [≥16 years]), leisure-time physical activity (MET·hours/day; as a continuous variable), and self-reported medical history of hypertension, diabetes, and dyslipidemia (yes or no) for males; for females, the same covariates were used as in males, plus age at menarche (≤12, 13, 14, ≥15 years), number of births (none, 1, 2, 3, ≥4), and menopausal status (pre-menopausal, menopausal [age at menopause <47, 47 to <50, 50 to <53, ≥53 years old]). Model 3: adjusted for covariates in Model 2 plus total energy intake (by quartile), and energy-adjusted intakes of green and yellow vegetables, light-colored vegetables, fruit, meat, rice, sodium, and dietary fiber (by quartile), and JDI score (points of 0–1, 2, 3, 4, 5, 6–7). For Model 4, we additionally adjusted for intakes of nutrients abundant in small fish, including n-3 HUFAs, calcium, vitamin

D, retinol, and carotene (by quartile) which might mediate the association between small fish and mortality. We did not conduct formal mediation analysis. We consider Model 3 to represent the main result in the present study. We confirmed the proportional hazards assumption in Model 3 by including each frequency category for the intake of small fish (1–3 times/month, 1–2 times/week, and ≥3 times/week) × time (continuous) interaction terms. The assumption was not violated (P >0.05) except for the interaction term for the small fish ≥3 times/week group × time in the analysis of male cancer mortality (P = 0.04). We also assessed the interaction between sex and intake of small fish on the mortality risk with Model 3 including the cross-product term (i.e., sex [dichotomous] × category of small fish consumed [continuous]), representing the interaction. The adjustment variables in Model 3 were different between sexes. Thus, in this analysis, we excluded the female-specific variables (age at menarche, number of births, and menopausal status), and adjusted for smoking habit and alcohol consumption to the same category used in females (smoking habit: never, former [quit smoking ≥10, <10 years ago], current [<20, ≥20 cigarettes/day]); alcohol consumption: never, former, current [<23, ≥23 g/day ethanol]). The total energy intake and the intakes of food groups and nutrients were adjusted for sex-specific quartiles. The JDI was calculated with the sex-specific median for the entire population of this study.

We analyzed 80,250 participants (34,169 males and 46,081 females), additionally excluding 552 participants who died 1 to 3 years after baseline measurements, using the same covariates as in Model 3. The participants who died within one year had been already excluded (Figure 1). This analysis was added to consider the influence of diseases that might have existed at baseline over a longer period than that considered in Model 3 (3 years versus 1 year). We further analyzed 75,121 participants (32,316 males and 42,805 females), excluding 5,681 participants from the Aichi Cancer Center using the same covariates as in Model 3 because they might have included undiagnosed cancer patients at baseline. Additionally, we performed stratified analyses by age (≥60, <60 years old), smoking status (never, [former or current]), and JDI score (≤3, ≥4 points), with adjustment for the same covariates as in Model 3. Effects of interactions between stratification variables and intake of small fish on the mortality risk were assessed with Model 3 including the cross-product term (i.e., stratification factors [dichotomous] × category of small fish consumed [continuous]), representing the interaction. Lastly, we considered the intake of non-small fish (raw fish, grilled fish, and boiled fish; do not include other seafood items) for the association of the intake of small fish with all-cause, cancer, CVD, and other-cause mortality using the same covariates as in Model 3 by further adjustment

for the frequency of the intake of non-small fish (<3 times/week, 3–4 times/week, 5–6 times/week, and ≥1 time/day), excluding 115 participants (34 males and 81 females) with missing data for the intake of non-small fish.

Participants with missing data for covariates were included as additional categories in the analysis. A two-tailed P value <0.05 was considered statistically significant. All statistical analyses were conducted using the SPSS software, version 28 (IBM, Armonk, NY, USA) and Stata/SE17 (StataCorp, Lakeway, TX, USA).

Results

Characteristics of participants

Tables 1 and 2 present the baseline characteristics according to the frequency of the intake of small fish in males and females, respectively. The mean age (SD) of 80,802 eligible participants (34,555 males and 46,247 females) was 54.7 (9.4) years. Those with frequent intake of small fish were more likely to be aged, non-lean, nonsmoker (never or former smoker), current drinker (in males), physically active, and having hypertension, and menopausal (in females). The distribution of education level and study area differed statistically significantly according to the frequency of the intake of small fish. The intake of small fish was positively correlated with the intake of all nutrients and foods (except for rice in males), total energy, and the JDI score.

All-cause mortality

During the 724,115 person-year follow-up (mean, 9.0 years), we identified 2,482 deaths (1,618 in males and 864 in females), including 1,495 cancer-related deaths (988 in males and 507 in females), 340 CVD deaths (204 in males and 136 in females), and 647 other-cause deaths (426 in males and 221 in females). In males, the top five sites for all cancer-related deaths were the lung (25.1%), pancreas (12.2%), stomach (10.9%), esophagus (9.3%), and colorectum (9.2%). In females, the top five sites were the lung (16.6%), pancreas (12.2%), colorectum (11.8%), breast (8.7%), and stomach (7.1%).

The association between the frequency of the intake of small fish and the risk of all-cause mortality by sex is shown in **Table 3**. In Models 1 and 2, with adjustment for multiple covariates, the intake of small fish was inversely associated with the risk of all-cause mortality in both the sexes. In Model 3, with further adjustment for energy-adjusted intake of foods and nutrients, and JDI score, the inverse association remained statistically significant in females,

but not in males. The multivariable-adjusted HRs (95% CIs) in females were 0.68 (0.55–0.85) for intakes 1–3 times/month, 0.72 (0.57–0.90) for 1–2 times/week, and 0.69 (0.54–0.88) for ≥3 times/week, compared with the rare intake (*P* for trend = 0.041). The corresponding HRs (95% CIs) in males were 0.81 (0.69–0.94), 0.84 (0.71–0.99), and 0.87 (0.73–1.05), respectively (*P* for trend = 0.391). In Model 4, with an additional adjustment for the energy-adjusted intake of nutrients abundant in small fish, the inverse association between the intake of small fish and all-cause mortality was observed in females although the HR for intake ≥3 times/week was higher than that in Model 3. No statistically significant association was observed in males in Model 4.

In the sensitivity analysis additionally excluding participants who died 1 to 3 years after the baseline survey and using the same covariates as in Model 3, the inverse association between the intake of small fish and all-cause mortality was almost unchanged in females. The HRs (95% CIs) were 0.67 (0.53–0.86) for intakes 1–3 times/month, 0.74 (0.57–0.94) for 1–2 times/week, and 0.67 (0.51–0.88) for ≥3 times/week, compared with the rare intake (*P* for trend = 0.047). No statistically significant trend in the association was observed in males. The HRs (95% CIs) were 0.82 (0.69–0.98) for intakes 1–3 times/month, 0.83 (0.69–0.99) for 1–2 times/week, and 0.90 (0.73–1.11) for ≥3 times/week, compared with the rare intake (*P* for trend = 0.560). In the analysis excluding participants from the Aichi Cancer Center and using the same covariates as in Model 3, the inverse association between the intake of small fish and all-cause mortality was also observed in females. The HRs (95% CIs) were 0.71 (0.56–0.90) for intakes 1–3 times/month, 0.76 (0.59–0.98) for 1–2 times/week, and 0.68 (0.51–0.89) for ≥3 times/week, compared with the rare intake (*P* for trend = 0.041). No statistically significant association was observed in males. The HRs (95% CIs) were 0.87 (0.73–1.04) for intakes 1–3 times/month, 0.91 (0.75–1.09) for 1–2 times/week, and 0.99 (0.81–1.22) for ≥3 times/week, compared with the rare intake (*P* for trend = 0.753). The *P* value for interaction between the intake of small fish and sex for all-cause mortality was not statistically significant (*P* for interaction = 0.238).

Cause-specific mortality

The associations between the frequency of the intake of small fish and the risk of cancer, CVD, and other-cause mortality by sex are also shown in Table 3. In Model 3, the intake of small fish was associated with a statistically significant decrease in the risk of cancer mortality, and a linear trend was observed in females. The multivariable-adjusted HRs (95% CIs) were 0.72 (0.54–0.96) for intakes 1–3 times/month, 0.71 (0.53–0.96) for 1–2 times/week, and 0.64

(0.46–0.89) for ≥3 times/week, compared with the rare intake (*P* for trend = 0.027). The association in males was not statistically significant, although its direction was the same as that in females. In Model 4, with an additional adjustment for the energy-adjusted intake of nutrients abundant in small fish, the inverse association between the intake of small fish and cancer mortality remained statistically significant in females. No statistically significant association was observed in males. In the sensitivity analysis additionally excluding participants who died 1 to 3 years after the baseline survey and using the same covariates as in Model 3, the inverse association between the intake of small fish and cancer mortality was almost unchanged in females, whereas no association was detected in males. The HRs (95% CIs) in females were 0.77 (0.55–1.07) for intakes 1–3 times/month, 0.76 (0.54–1.07) for 1–2 times/week, and 0.63 (0.43–0.93) for ≥3 times/week, compared with the rare intake (*P* for trend = 0.039). The corresponding HRs (95% CIs) in males were 0.91 (0.72–1.16), 0.84 (0.65–1.09), and 0.91 (0.69–1.22), respectively (*P* for trend = 0.460). In the analysis excluding participants from the Aichi Cancer Center and using the same covariates as in Model 3, the inverse association between the intake of small fish ≥3 times/week and cancer mortality was statistically significant in females, but not in males. The HRs (95% CIs) in females were 0.79 (0.56–1.12) for intakes 1–3 times/month, 0.83 (0.58–1.18) for 1–2 times/week, and 0.66 (0.45–0.98) for ≥3 times/week, compared with the rare intake (*P* for trend = 0.081). The corresponding HRs (95% CIs) in males were 0.98 (0.76–1.26), 0.91 (0.70–1.20), and 1.00 (0.74–1.34), respectively (*P* for trend = 0.827). The intake of small fish was not clearly associated with the risk of CVD and other-cause mortality in both sexes. The *P* values for interaction between the intake of small fish and sex for the risk were 0.167 for cancer mortality, 0.867 for CVD mortality, and 0.905 for other-cause mortality, none of which was statistically significant.

Stratified analysis

Tables 4 and 5 show the HRs (95% CIs) for all-cause and cancer mortality according to the frequency of the intake of small fish in the analyses stratified by age, smoking status, and JDI score. In the analysis stratified by age, no remarkable age-dependent differences were found in the directions of the associations between the intake of small fish and all-cause and cancer mortality in both the sexes. The *P* values for interaction between the intake of small fish and age for the risk were 0.289 for all-cause mortality and 0.175 for cancer mortality in males. The corresponding *P* values in females were 0.827 for all-cause mortality and 0.909 for cancer

mortality. As for the smoking status, the intake of small fish was inversely associated with the risk of all-cause and cancer mortality, especially in never-smoking females. The multivariable-adjusted HRs (95% CIs) for all-cause mortality were 0.60 (0.47–0.76) for intakes 1–3 times/month, 0.62 (0.48–0.79) for 1–2 times/week, and 0.61 (0.47–0.79) for ≥3 times/week, compared with the rare intake (P for trend = 0.011). The corresponding HRs (95% CIs) for cancer mortality were 0.62 (0.46–0.85), 0.59 (0.43–0.82), and 0.53 (0.37–0.75), respectively (P for trend = 0.003). In males, no statistically significant association was observed in either smokers or never smokers. The P value for interaction between the intake of small fish and smoking status for the risk was 0.268 for all-cause mortality and 0.059 for cancer mortality in females. The corresponding P values in males were 0.892 for all-cause mortality and 0.400 for cancer mortality. Regarding the analysis stratified by the JDI score, the inverse associations between the intake of small fish and the risk of all-cause and cancer mortality were stronger in females with a high-JDI score (≥4 points). The multivariable-adjusted HRs (95% CIs) for all-cause mortality were 0.61 (0.45–0.83) for intakes 1–3 times/month, 0.63 (0.46–0.84) for 1–2 times/week, and 0.56 (0.41–0.77) for ≥3 times/week, compared with the rare intake (P for trend = 0.008). The corresponding HRs (95% CIs) for cancer mortality were 0.61 (0.41–0.93), 0.59 (0.40–0.89), and 0.52 (0.34–0.79), respectively (P for trend = 0.016). In males, the intake of small fish was inversely associated with the risk of all-cause and cancer mortality in the low-JDI score (≤3 points) group. The multivariable-adjusted HRs (95% CIs) for all-cause mortality were 0.73 (0.60–0.88) for intakes 1–3 times/month, 0.68 (0.54–0.86) for 1–2 times/week, and 0.84 (0.61–1.15) for ≥3 times/week, compared with the rare intake (P for trend = 0.038). The corresponding HRs (95% CI) for cancer mortality were 0.70 (0.55–0.89), 0.57 (0.42–0.77), and 0.60 (0.39–0.91), respectively (P for trend <0.001). Tests of interactions between the intake of small fish and JDI score for all-cause and cancer mortality were statistically significant in males, but not in females. The P values for the interaction of all-cause and cancer mortality were 0.045 and 0.002 in males, and 0.525 and 0.621 in females, respectively.

Intake of small and non-small fish

Supplemental Table 1 summarizes the associations between the frequency of the intake of small and non-small fish and the risk of all-cause, cancer, CVD, and other-cause mortality by sex in the analysis, adjusting for the intake of small and non-small fish each other in addition to the covariates in Model 3. The intakes of both small and non-small fish were not statistically significantly associated with the risk of each mortality in males. In females, the intake of small fish was statistically significantly associated with a lower risk of all-cause and cancer mortality, but not with CVD and other-cause mortality, even after considering the intake of non-small fish. The multivariable-adjusted HRs (95% CIs) for all-cause mortality according to the frequency of the intake of small fish were 0.68 (0.55–0.85) for intakes 1–3 times/month, 0.72 (0.58–0.91) for 1–2 times/week, and 0.69 (0.54–0.89) for ≥3 times/week, compared with the rare intake (P for trend = 0.050). The corresponding HRs (95% CIs) for cancer mortality were 0.72 (0.54–0.96), 0.72 (0.53–0.97), and 0.65 (0.46–0.90), respectively (P for trend = 0.034). Once a day or more frequent intake of non-small fish was associated with lower all-cause mortality in females.

Discussion

In this large prospective study, the frequent intake of small fish was associated with a lower all-cause and cancer mortality in females. The association in males was not statistically significant, although its direction between the intake of small fish and cancer mortality was the same as in females. Regarding the association between the intake of small fish and all-cause mortality in males, the HRs were lower for intakes 1–3 times/month or more, compared with the rare intake. The intake of small fish was not associated with CVD mortality in both sexes. To our knowledge, this is the first study to demonstrate the association between intake of small fish and the risk of all-cause and cause-specific mortality. Small fish can be a component of a healthy diet. They are a good source of micronutrients such as calcium, vitamins, and fatty acids, when consumed with bones and organs [2, 3, 5, 6]. With regard to the relationship between nutrients in small fish and mortality risk, calcium intake is inversely associated with the risk of all-cause and CVD mortality, and some proportion of cancer mortality, such as mortality among patients with early-stage lung cancer [7, 32, 33]; however, some reports suggest that high intake of calcium can increase the risk of cancer and CVD mortality [7, 32, 34]. Thus, appropriate calcium intake, considering individual health status, such as pre-existing diseases (cancer, osteoporosis, and heart disease), has been recommended [7].

Because calcium from small fish with bones is highly bioavailable, small fish are a useful source of calcium[5, 35]. Another mechanism for the protective effect of small fish on mortality risk may involve the antitumor effects of vitamins A and D as well as n-3 polyunsaturated fatty acids (n-3 PUFAs). Focusing on the major sites associated with cancer death in Japan, recent meta-analyses have shown inverse associations between dietary vitamin A intake and the risk of lung, pancreatic, gastric, and breast cancers [36-40]. Vitamin D intake or serum 25-hydroxyvitamin D [25(OH)D] level has also been reported to be inversely associated with the risk of lung, breast, and colorectal cancer morbidity and mortality [8, 41-44]. N-3 PUFA intake has been related to a reduced risk of breast cancer and is also inversely related to all-cause and CVD mortality in some reports; however, the association is still controversial [18, 45-49].

In this study, an association between the intake of small fish and all-cause and cancer mortality was observed in females, and this association remained even after adjustment for female-specific factors, including age at menarche, number of births, and menopausal status. One of the reasons underlying the difference in the effects of consumption of small fish on the risk of all-cause and cancer mortality between sexes in this study might be the difference in the cancer type causing cancer mortality among sexes; however, other reasons are unknown. The sex-based difference in the association between the intake of small fish and alcohol and/or other food consumption might provide another explanation although we did consider alcohol drinking and food consumption in the multivariable models. The P values for interaction between the intake of small fish and sex for the risk were not statistically significant. The sex-difference, if any, could not be so large.

Vitamin A contributes to the prevention of cancer through antioxidant activity, induction of detoxifying enzymes, and regulation of genes involved in cell morphogenesis, differentiation, and proliferation [9, 37]. Vitamin D exerts antitumor effects by contact inhibition of proliferation, cell cycle stabilization, promotion of apoptosis, and anti-neoangiogenesis [8]. N-3 HUFAs suppress the progression of carcinogenesis and metastasis through the production of lipid peroxides and increased apoptosis of cancer cells [50]. In Model 4 (Table 3), the adjustment for intakes of these nutrients based on the abovementioned findings weakened the inverse association between the intake of small fish and all-cause and cancer mortality. However, the association remained statistically significant in females. This suggests that the effects of these nutrients only partially explain the association of mortality risk, and other or unknown nutrients or physiologically active substances might exert protective effects. Some

small fish are rich in magnesium [4]; however, this was not adjusted for in this study due to the limitation of FFQ. Magnesium intake reduces the risk of lung cancer [12]. Serum magnesium is also inversely correlated with all-cause and cancer mortality [51]. The intake of small fish is expected to contribute to a well-balanced intake of micronutrients, such as calcium, vitamins A and D, n-3 PUFAs, and magnesium.

Participants who consumed higher amounts of small fish could have had a healthier diet as shown in Tables 1 and 2, and demonstrated a lower mortality. To eliminate this confounding factor, we adjusted for the JDI score. The JDI score, which is a measure of the degree of adherence to the Japanese diet, is also an indicator of healthy dietary patterns as, in previous studies, higher JDI scores were reported to be associated with lower risk of all-cause and CVD mortality [30, 31]. Even after adjustment for the JDI score, the inverse association between the intake of small fish and all-cause and cancer mortality was scarcely altered in females, which suggests that the intake of small fish reduces the risk of all-cause and cancer mortality, independent of a healthy diet. Furthermore, in the analysis adjusting for the intake of non-small fish, the inverse association between the intake of small fish and the risk of all-cause and cancer mortality remained statistically significant in females. This suggests that intake of small fish is associated with a reduced risk of all-cause and cancer mortality, independent of the intake of non-small fish.

The stratified analysis with respect to the smoking status revealed that the intake of small fish was inversely associated with the risk of all-cause and cancer mortality in female never smokers. We also adjusted for comprehensive smoking variables. These support that confounding by smoking is unlikely. The results of the analysis stratified by the JDI score showed that the inverse association between the intake of small fish and all-cause and cancer mortality was stronger in the high-JDI score group among females. In males, the inverse association was found in the low-JDI score group, but not found in all the males. Although the reason for this sex-based difference is unclear, for males with unhealthy dietary patterns, the intake of small fish may help compensate for the lack of nutrients in poor-quality diets.

The strengths of the present study are the large sample size, prospective design, and the extensive adjustment for potentially important confounding factors. Nonetheless, this study has several limitations. First, changes in eating habits or lifestyle factors during the follow-up period could not be considered because the questionnaire was answered only once at the baseline survey by a considerable proportion of participants (40.8%). Second, the use of an FFQ inevitably lead to some misclassification of the intake of small fish, although the

questionnaire was validated based on dietary records. The validity was not good for several food groups and nutrients included as covariates. Third, residual confounding, such as socioeconomic status, cannot be completely ruled out, although we adjusted for many potential confounding factors. Fourth, the number of CVD death events might not be enough to conclude the association between intake of small fish and the risk of CVD mortality. Finally, because the study area is limited to Japan, our findings are not generalizable to other countries.

In conclusion, we suggest that the intake of small fish reduces the risk of all-cause and cancer mortality in Japanese females.

Authorship:

The authors' responsibilities were as follows—CK analyzed data and wrote the paper; TT analyzed data and extensively revised the paper; CK and KW designed research and had primary responsibility for final content; NI and CG provided essential materials; YT, Y. Kato, Y. Kubo, RO, MN, AH, JO, HI, Y. Nishida, CS, IO, YNK, Y. Nakamura, MK, DN, IS, SS, MW, EO, CO, KK, NT, NM, KA, SKK, KT, and KM conducted research. KM supervised the J-MICC Study. All authors read and approved the final manuscript.

Ethical Standards Disclosure:

This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving study participants were approved by the ethics committees of Nagoya University Graduate School of Medicine and other participating institutions in the J-MICC Study. Written informed consent was obtained from all the participants.

Data Sharing Plan

Based on the informed consent provided by the participants, some access restrictions apply, and the data cannot be made publicly available. Requests for data can be sent to Dr. Kenji Wakai, Department of Preventive Medicine, Nagoya University Graduate School of Medicine, Japan (e-mail: wakai@med.nagoya-u.ac.jp).

Abbreviations:

BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; FFQ, food frequency questionnaire; HR, hazard ratio; ICD-10, International Classification of Diseases and Related Health Problems, Tenth Revision; JDI, Japanese diet index; J-MICC, Japan Multi-Institutional Collaborative Cohort; KOPS, Kyushu and Okinawa Population Study; MET, metabolic equivalent; n-3 HUFAs, n-3 highly unsaturated fatty acids; n-3 PUHA, n-3 polyunsaturated fatty acids

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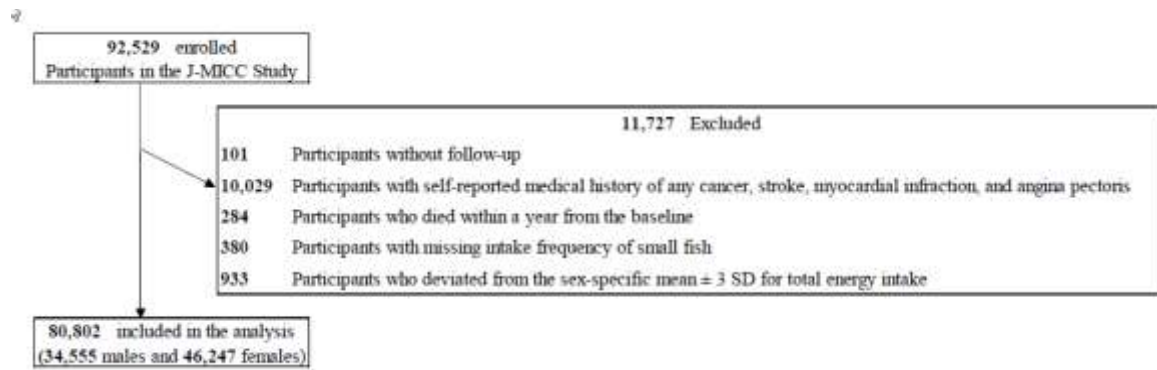
Figure 1: The flowchart for selection of participants for the present study

Abbreviation: J-MICC Study, Japan Multi-Institutional Collaborative Cohort Study

TABLE 1 Baseline characteristics in males according to the frequency of the intake of small fish*

	Rarely	1–3 times/month	1–2 times/week	≥3 times/week	Total	*P* value
Participants, n	5,046	14,579	9,890	5,040	34,555	
Age, years, mean, SD	52.8, 9.6	53.9, 9.4	56.5, 8.9	59.4, 8.2	55.3, 9.4	<0.001
Study area						
Kanto (Chiba)	373 (7.4)	1,227 (8.4)	683 (6.9)	292 (5.8)	2,575 (7.5)	<0.001
Chubu (Aichi Cancer Center, Okazaki, Shizuoka, Iga, Daiko, Shizuoka-Sakuragaoka)	1,573 (31.2)	5,553 (38.1)	4,050 (41.0)	1,886 (37.4)	13,062 (37.8)	
Kinki (Takashima, Kyoto)	485 (9.6)	1,389 (9.5)	973 (9.8)	540 (10.7)	3,387 (9.8)	
Shikoku (Tokushima)	215 (4.3)	596 (4.1)	347 (3.5)	144 (2.9)	1,302 (3.8)	
Kyushu and Okinawa (Fukuoka, Saga, Kagoshima, KOPS)	2,400 (47.6)	5,814 (39.9)	3,837 (38.8)	2,178 (43.2)	14,229 (41.2)	
BMI, kg/m^2						
18.5–24.9	3,238 (64.2)	9,803 (67.2)	6,730 (68.0)	3,394 (67.3)	23,165 (67.0)	<0.001
<18.5	168 (3.3)	377 (2.6)	241 (2.4)	104 (2.1)	890 (2.6)	
≥25.0	1,636 (32.4)	4,390 (30.1)	2,916 (29.5)	1,538 (30.5)	10,480 (30.3)	
Unknown	4 (0.1)	9 (0.1)	3 (0.0)	4 (0.1)	20 (0.1)	
Smoking habit						
Never	1,522 (30.2)	4,188 (28.7)	2,883 (29.2)	1,562 (31.0)	10,155 (29.4)	<0.001
Former, quit ≥10.0 years before	916 (18.2)	3,126 (21.4)	2,375 (24.0)	1,302 (25.8)	7,719 (22.3)	
Former, quit 5.0–9.9 years before	256 (5.1)	941 (6.5)	615 (6.2)	321 (6.4)	2,133 (6.2)	
Former, quit <5.0 years before	458 (9.1)	1,373 (9.4)	884 (8.9)	434 (8.6)	3,149 (9.1)	
Current, <20 cigarettes/day	511 (10.1)	1,420 (9.7)	933 (9.4)	421 (8.4)	3,285 (9.5)	
Current, 20–39 cigarettes/day	1,051 (20.8)	2,751 (18.9)	1,723 (17.4)	739 (14.7)	6,264 (18.1)	
Current, ≥40 cigarettes/day	205 (4.1)	424 (2.9)	222 (2.2)	121 (2.4)	972 (2.8)	
Unknown	127 (2.5)	356 (2.4)	255 (2.6)	140 (2.8)	878 (2.5)	
Alcohol consumption						

Never	1,378 (27.3)	2,948 (20.2)	1,822 (18.4)	838 (16.6)	6,986 (20.2)	<0.001
Former	209 (4.1)	397 (2.7)	256 (2.6)	183 (3.6)	1,045 (3.0)	
Current, <23.0 g/day ethanol	1,678 (33.3)	5,420 (37.2)	3,560 (36.0)	1,692 (33.6)	12,350 (35.7)	
Current, 23.0–45.9 g/day ethanol	865 (17.1)	2,977 (20.4)	2,122 (21.5)	1,165 (23.1)	7,129 (20.6)	
Current, ≥46.0 g/day ethanol	910 (18.0)	2,821 (19.3)	2,120 (21.4)	1,157 (23.0)	7,008 (20.3)	
Unknown	6 (0.1)	16 (0.1)	10 (0.1)	5 (0.1)	37 (0.1)	
Education level						<0.001
Junior high school (≤9 years)	380 (7.5)	869 (6.0)	767 (7.8)	575 (11.4)	2,591 (7.5)	
High school (10–12 years)	1,550 (30.7)	4,372 (30.0)	2,932 (29.6)	1,425 (28.3)	1,0279 (29.7)	
Junior college or vocational school (13–15 years)	478 (9.5)	1,338 (9.2)	813 (8.2)	390 (7.7)	3,019 (8.7)	
College, university or above (≥16 years)	1,447 (28.7)	5,087 (34.9)	3,213 (32.5)	1,304 (25.9)	11,051 (32.0)	
No question in the questionnaire	1,176 (23.3)	2,848 (19.5)	2,127 (21.5)	1,319 (26.2)	7,470 (21.6)	
Others or unknown	15 (0.3)	65 (0.4)	38 (0.4)	27 (0.5)	145 (0.4)	
Leisure-time physical activity, MET·hours/day, mean, SD	1.6, 2.9	2.0, 3.1	2.4, 3.6	2.7, 3.8	2.1, 3.4	<0.001
Hypertension						<0.001
No	4,034 (79.9)	11,522 (79.0)	7,565 (76.5)	3,698 (73.4)	26,819 (77.6)	
Yes	998 (19.8)	3,024 (20.7)	2,304 (23.3)	1,334 (26.5)	7,660 (22.2)	
Unknown	14 (0.3)	33 (0.2)	21 (0.2)	8 (0.2)	76 (0.2)	
Diabetes						<0.001
No	4,633 (91.8)	13,484 (92.5)	9,000 (91.0)	4,523 (89.7)	31,640 (91.6)	
Yes	401 (7.9)	1,069 (7.3)	875 (8.8)	506 (10.0)	2,851 (8.3)	
Unknown	12 (0.2)	26 (0.2)	15 (0.2)	11 (0.2)	64 (0.2)	
Dyslipidemia						0.452
No	4,278 (84.8)	12,371 (84.9)	8,321 (84.1)	4,309 (85.5)	29,279 (84.7)	
Yes	752 (14.9)	2,154 (14.8)	1,535 (15.5)	713 (14.1)	5,154 (14.9)	
Unknown	16 (0.3)	54 (0.4)	34 (0.3)	18 (0.4)	122 (0.4)	
Small fish intake†, g/1000 kcal/day, median, IQR	0.0, 0–0	1.1, 1.0–1.2	2.1, 1.9–2.3	5.7, 4.9–8.4	1.3, 1.0–2.2	<0.001

Non-small fish intake†, ‡, g/1000 kcal/day, median, IQR	8.1, 5.5–17.9	8.9, 7.1–19.0	16.3, 7.7–20.5	19.7, 15.7–29.0	13.8, 7.3–20.3	<0.001
Energy intake, kcal/day, median, IQR	1,813.7, 1,613.7–2,021.3	1,849.8, 1,673.7–2,050.4	1,911.2, 1,741.7–2,103.7	1,961.6, 1,787.4–2,164.8	1,880.6, 1,697.4–2,081.4	<0.001
Rice intake†, g/1000 kcal/day, median, IQR	229.6, 180.1–278.5	228.3, 182.7–274.4	234.2, 188.3–278.3	238.3, 191.5–278.7	231.3, 185.3–276.9	<0.001
Meat intake†, g/1000 kcal/day, median, IQR	15.9, 10.9–24.1	16.2, 11.9–24.3	16.7, 12.8–24.8	17.6, 12.4–27.2	16.5, 12.1–24.8	<0.001
Fruits intake†, g/1000 kcal/day, median, IQR	10.3, 4.8–20.7	13.7, 8.8–27.8	17.5, 10.1–36.3	25.1, 12.3–47.2	15.4, 9.0–33.0	<0.001
Green and yellow vegetables intake†, g/1000 kcal/day, median, IQR	18.3, 11.4–30.3	21.9, 15.0–34.3	27.5, 18.6–41.1	35.6, 22.1–53.1	24.4, 16.0–38.7	<0.001
Light-colored vegetables intake†, g/1000 kcal/day, median, IQR	20.4, 12.6–32.3	22.8, 14.6–33.8	27.2, 17.5–38.8	34.7, 23.4–48.0	25.2, 15.7–37.4	<0.001
Sodium intake, mg/1000 kcal/day, median, IQR	862.4, 705.7–1,060.3	893.6, 749.3–1,073.1	922.5, 777.6–1,109.3	1024.3, 865.1–1,235.8	916.4, 765.3–1,105.8	<0.001
Dietary fiber intake, g/1000 kcal/day, median, IQR	4.7, 3.9–5.6	4.9, 4.2–5.8	5.2, 4.4–6.2	5.9, 4.8–7.0	5.1, 4.3–6.1	<0.001
Calcium intake, mg/1000 kcal/day, median, IQR	226.3, 185.7–276.6	236.6, 197.9–287.3	249.1, 208.0–302.6	284.2, 235.2–344.1	245.2, 202.8–299.7	<0.001
Vitamin D intake, μg/1000 kcal/day, median, IQR	2.6, 2.0–3.7	3.0, 2.5–4.2	3.9, 2.9–4.8	5.6, 4.6–7.0	3.6, 2.6–4.8	<0.001
N-3 highly unsaturated fatty acids intake, mg/1000 kcal/day, median, IQR	269.7, 216.3–400.0	309.6, 250.2–438.2	394.4, 283.9–486.9	516.2, 421.7–655.8	361.8, 262.4–484.6	<0.001

Retinol intake,						
μg/1000 kcal/day, median, IQR	343.8, 276.2–489.0	428.4, 308.4–585.9	491.1, 342.3–638.9	537.2, 380.4–703.3	447.0, 315.6–608.5	<0.001
Carotene intake,						
μg/1000 kcal/day, median, IQR	1,199.7, 962.6–1,574.6	1,267.3, 1,036.9–1,642.7	1,406.8, 1,116.3–1,825.9	1,624.3, 1,218.8–2,127.9	1,336.3, 1,061.0–1,764.9	<0.001
JDI score, points						
0–1	1,245 (24.7)	2,222 (15.2)	603 (6.1)	68 (1.3)	4,138 (12.0)	<0.001
2	1,157 (22.9)	2,787 (19.1)	1,054 (10.7)	252 (5.0)	5,250 (15.2)	
3	1,054 (20.9)	3,316 (22.7)	1,853 (18.7)	586 (11.6)	6,809 (19.7)	
4	872 (17.3)	3,079 (21.1)	2,448 (24.8)	1,086 (21.5)	7,485 (21.7)	
5	507 (10.0)	2,141 (14.7)	2,428 (24.6)	1,542 (30.6)	6,618 (19.2)	
6–7	211 (4.2)	1,034 (7.1)	1,504 (15.2)	1,506 (29.9)	4,255 (12.3)	

Abbreviations: BMI, body mass index; IQR, Interquartile range; JDI, Japanese diet index; KOPS, Kyushu and Okinawa Population Study; MET, metabolic equivalent; SD, standard deviation.

*Values are numbers (percentages) unless indicated otherwise.

†Food consumption of the total population including nonconsumers was used.

‡Excluded 34 males with missing data for the intake of non-small fish.

TABLE 2 Baseline characteristics in females according to the frequency of the intake of small fish*

	Rarely	1–3 times/month	1–2 times/week	≥3 times/week	Total	*P* value
Participants, n	5,599	17,562	13,746	9,340	46,247	
Age, years, mean, SD	51.0, 9.6	52.2, 9.2	55.2, 9.1	58.7, 8.2	54.3, 9.4	<0.001
Study area						
Kanto (Chiba)	537 (9.6)	1,962 (11.2)	1,422 (10.3)	822 (8.8)	4,743 (10.3)	<0.001
Chubu (Aichi Cancer Center, Okazaki, Shizuoka, Iga, Daiko, Shizuoka-Sakuragaoka)	1,572 (28.1)	5,563 (31.7)	4,397 (32.0)	2,516 (26.9)	14,048 (30.4)	
Kinki (Takashima, Kyoto)	520 (9.3)	1,957 (11.1)	1,707 (12.4)	1,190 (12.7)	5,374 (11.6)	
Shikoku (Tokushima)	174 (3.1)	362 (2.1)	260 (1.9)	134 (1.4)	930 (2.0)	
Kyushu and Okinawa (Fukuoka, Saga, Kagoshima, KOPS)	2,796 (49.9)	7,718 (43.9)	5,960 (43.4)	4,678 (50.1)	21,152 (45.7)	
BMI, kg/m^2						
18.5–24.9	3,930 (70.2)	12,810 (72.9)	10,089 (73.4)	6,651 (71.2)	33,480 (72.4)	<0.001
<18.5	587 (10.5)	1,649 (9.4)	1,234 (9.0)	787 (8.4)	4,257 (9.2)	
≥25.0	1,070 (19.1)	3,078 (17.5)	2,400 (17.5)	1,893 (20.3)	8,441 (18.3)	
Unknown	12 (0.2)	25 (0.1)	23 (0.2)	9 (0.1)	69 (0.1)	
Smoking habit						
Never	4,397 (78.5)	14,577 (83.0)	11,978 (87.1)	8,414 (90.1)	39,366 (85.1)	<0.001
Former, quit ≥10.0 years before	206 (3.7)	652 (3.7)	423 (3.1)	235 (2.5)	1,516 (3.3)	
Former, quit <10.0 years before	273 (4.9)	696 (4.0)	413 (3.0)	204 (2.2)	1,586 (3.4)	
Current, <20 cigarettes/day	395 (7.1)	976 (5.6)	523 (3.8)	258 (2.8)	2,152 (4.7)	
Current, ≥20 cigarettes/day	253 (4.5)	468 (2.7)	265 (1.9)	144 (1.5)	1,130 (2.4)	
Unknown	75 (1.3)	193 (1.1)	144 (1.0)	85 (0.9)	497 (1.1)	
Alcohol consumption						
Never	3,423 (61.1)	10,118 (57.6)	8,359 (60.8)	6,107 (65.4)	28,007 (60.6)	<0.001
Former	142 (2.5)	328 (1.9)	206 (1.5)	158 (1.7)	834 (1.8)	
Current, <23.0 g/day ethanol	1,666 (29.8)	6,040 (34.4)	4,488 (32.6)	2,611 (28.0)	14,805 (32.0)	
Current, ≥23.0 g/day ethanol	356 (6.4)	1,057 (6.0)	672 (4.9)	450 (4.8)	2,535 (5.5)	
Unknown	12 (0.2)	19 (0.1)	21 (0.2)	14 (0.1)	66 (0.1)	

Education level						
Junior high school (≤9 years)	331 (5.9)	911 (5.2)	878 (6.4)	888 (9.5)	3,008 (6.5)	<0.001
High school (10–12 years)	1,776 (31.7)	5,809 (33.1)	4,571 (33.3)	3,002 (32.1)	15,158 (32.8)	
Junior college or vocational school (13–15 years)	1,373 (24.5)	4,999 (28.5)	3,440 (25.0)	1,978 (21.2)	11,790 (25.5)	
College, university or above (≥16 years)	535 (9.6)	1,993 (11.3)	1,461 (10.6)	738 (7.9)	4,727 (10.2)	
No question in the questionnaire	1,564 (27.9)	3,792 (21.6)	3,337 (24.3)	2,687 (28.8)	11,380 (24.6)	
Others or unknown	20 (0.4)	58 (0.3)	59 (0.4)	47 (0.5)	184 (0.4)	
Leisure-time physical activity,						
MET·hours/day, mean, SD	1.3, 2.5	1.6, 2.7	2.0, 3.0	2.4, 3.4	1.9, 2.9	<0.001
Hypertension						
No	4,928 (88.0)	15,302 (87.1)	11,527 (83.9)	7,604 (81.4)	39,361 (85.1)	<0.001
Yes	657 (11.7)	2,219 (12.6)	2,197 (16.0)	1,711 (18.3)	6,784 (14.7)	
Unknown	14 (0.3)	41 (0.2)	22 (0.2)	25 (0.3)	102 (0.2)	
Diabetes						
No	5,418 (96.8)	17,057 (97.1)	13,304 (96.8)	8,952 (95.8)	44,731 (96.7)	<0.001
Yes	166 (3.0)	476 (2.7)	424 (3.1)	366 (3.9)	1,432 (3.1)	
Unknown	15 (0.3)	29 (0.2)	18 (0.1)	22 (0.2)	84 (0.2)	
Dyslipidemia						
No	4,881 (87.2)	15,178 (86.4)	11,590 (84.3)	7,723 (82.7)	39,372 (85.1)	<0.001
Yes	698 (12.5)	2,332 (13.3)	2,107 (15.3)	1,580 (16.9)	6,717 (14.5)	
Unknown	20 (0.4)	52 (0.3)	49 (0.4)	37 (0.4)	158 (0.3)	
Age at menarche, years						
≤12	1,977 (35.3)	6,432 (36.6)	4,221 (30.7)	2,345 (25.1)	14,975 (32.4)	<0.001
13	1,368 (24.4)	4,450 (25.3)	3,478 (25.3)	2,278 (24.4)	11,574 (25.0)	
14	1,259 (22.5)	4,015 (22.9)	3,464 (25.2)	2,467 (26.4)	11,205 (24.2)	
≥15	940 (16.8)	2,579 (14.7)	2,501 (18.2)	2,202 (23.6)	8,222 (17.8)	
Unknown	55 (1.0)	86 (0.5)	82 (0.6)	48 (0.5)	271 (0.6)	
Number of births						
None	697 (12.4)	1,528 (8.7)	864 (6.3)	594 (6.4)	3,683 (8.0)	<0.001
1	653 (11.7)	2,030 (11.6)	1,423 (10.4)	879 (9.4)	4,985 (10.8)	

2	2,091 (37.3)	7,669 (43.7)	6,258 (45.5)	4,200 (45.0)	20,218 (43.7)	
3	1,193 (21.3)	4,282 (24.4)	3,677 (26.7)	2,596 (27.8)	11,748 (25.4)	
≥4	473 (8.4)	1,084 (6.2)	944 (6.9)	739 (7.9)	3,240 (7.0)	
Unknown	492 (8.8)	969 (5.5)	580 (4.2)	332 (3.6)	2,373 (5.1)	
Menopausal status						
Pre-menopausal	2,823 (50.4)	8,104 (46.1)	4,447 (32.4)	1,740 (18.6)	17,114 (37.0)	<0.001
Menopause at <47 years old	592 (10.6)	1,689 (9.6)	1,524 (11.1)	1,203 (12.9)	5,008 (10.8)	
Menopause at 47 to <50 years old	516 (9.2)	1,639 (9.3)	1,525 (11.1)	1,204 (12.9)	4,884 (10.6)	
Menopause at 50 to <53 years old	1,012 (18.1)	3,732 (21.3)	3,753 (27.3)	3,031 (32.5)	11,528 (24.9)	
Menopause at ≥53 years old	593 (10.6)	2,242 (12.8)	2,352 (17.1)	2,045 (21.9)	7,232 (15.6)	
Unknown	63 (1.1)	156 (0.9)	145 (1.1)	117 (1.3)	481 (1.0)	
Small fish intake†,						
g/1000 kcal/day, median, IQR	0.0, 0–0	1.0, 0.9–1.1	1.9, 1.8–2.1	5.6, 4.7–8.4	1.5, 0.9–2.2	<0.001
Non-small fish intake†, ‡,						
g/1000 kcal/day, median, IQR	8.6, 6.7–19.2	10.9, 7.8–20.4	18.3, 8.5–22.5	20.4, 17.0–30.7	17.7, 8.1–22.4	<0.001
Energy intake,						
kcal/day, median, IQR	1,478.4, 1,322.2–1,613.0	1,512.3, 1,375.0–1,636.4	1,549.3, 1,416.8–1,673.2	1,591.1, 1,457.6–1,718.7	1,535.0, 1,394.7–1,664.8	<0.001
Rice intake†,						
g/1000 kcal/day, median, IQR	176.1, 128.5–217.8	177.1, 134.8–218.3	182.1, 141.3–224.9	192.1, 150.1–235.1	181.6, 138.8–224.1	<0.001
Meat intake†,						
g/1000 kcal/day, median, IQR	22.1, 15.2–32.7	23.0, 16.5–33.1	23.8, 16.8–34.1	24.2, 16.0–35.5	23.3, 16.4–33.9	<0.001
Fruits intake†,						
g/1000 kcal/day, median, IQR	20.3, 10.9–49.1	25.5, 14.0–56.1	39.2, 20.1–66.5	53.0, 23.4–82.8	35.1, 16.5–63.9	<0.001
Green and yellow vegetables intake†,						
g/1000 kcal/day, median, IQR	33.4, 21.7–52.3	38.6, 25.9–56.6	47.6, 32.7–67.7	59.3, 41.3–82.2	44.5, 29.0–65.5	<0.001
Light-colored vegetables intake†,						
g/1000 kcal/day, median, IQR	37.6, 24.6–53.1	41.1, 28.5–56.2	46.8, 33.8–62.8	55.7, 41.1–73.7	45.2, 31.3–61.7	<0.001
Sodium intake,						
mg/1000 kcal/day, median, IQR	1,029.2, 866.8–1,213.5	1,068.5, 919.2–1,243.1	1,105.5, 961.6–1,280.6	1,205.6, 1,042.2–1,408.8	1,102.5, 946.7–1,287.0	<0.001

Dietary fiber intake,						
g/1000 kcal/day, median, IQR	6.5, 5.6–7.7	6.8, 5.9–8.0	7.4, 6.4–8.7	8.3, 7.0–9.7	7.2, 6.1–8.5	<0.001
Calcium intake,						
mg/1000 kcal/day, median, IQR	312.2, 254.5–378.8	326.0, 271.8–389.6	342.9, 290.6–406.7	381.6, 323.5–452.1	340.7, 283.9–407.7	<0.001
Vitamin D intake,						
µg/1000 kcal/day, median, IQR	3.0, 2.5–4.3	3.8, 3.0–4.8	4.6, 3.5–5.5	6.2, 5.2–7.6	4.5, 3.2–5.7	<0.001
N-3 highly unsaturated fatty acids intake,						
mg/1000 kcal/day, median, IQR	313.5, 258.1–453.7	386.3, 294.8–495.4	460.3, 338.5–555.1	563.7, 470.4–712.7	446.2, 313.4–559.3	<0.001
Retinol intake,						
µg/1000 kcal/day, median, IQR	484.6, 380.1–660.4	560.2, 421.3–761.0	640.1, 469.5–834.9	710.4, 525.1–922.6	602.3, 444.0–808.8	<0.001
Carotene intake,						
µg/1000 kcal/day, median, IQR	1,829.0, 1,419.8–2,421.8	1,952.6, 1,531.6–2,492.0	2,180.5, 1,714.6–2,766.8	2,510.6, 1,965.1–3,166.5	2,114.9, 1,628.8–2,720.8	<0.001
JDI score, points						
0–1	1,368 (24.4)	2,431 (13.8)	669 (4.9)	116 (1.2)	4,584 (9.9)	<0.001
2	1,219 (21.8)	3,264 (18.6)	1,521 (11.1)	343 (3.7)	6,347 (13.7)	
3	1,233 (22.0)	4,185 (23.8)	2,655 (19.3)	963 (10.3)	9,036 (19.5)	
4	958 (17.1)	3,927 (22.4)	3,624 (26.4)	2,013 (21.6)	10,522 (22.8)	
5	576 (10.3)	2,624 (14.9)	3,323 (24.2)	3,021 (32.3)	9,544 (20.6)	
6–7	245 (4.4)	1,131 (6.4)	1,954 (14.2)	2,884 (30.9)	6,214 (13.4)	

Abbreviations: BMI, body mass index; IQR, Interquartile range; JDI, Japanese diet index; KOPS, Kyushu and Okinawa Population Study; MET, metabolic equivalent; SD, standard deviation.

*Values are numbers (percentages) unless indicated otherwise.

†Food consumption of the total population including non-consumers was used.

‡Excluded 81 females with missing data for the intake of non-small fish.

TABLE 3 Multivariable-adjusted HRs (95% CI) for all-cause, cancer, CVD, and other-cause mortality by sex according to the frequency of the intake of small fish

	Male					Female					P for interaction between sex and intake‖
	Rarely	1–3 times/month	1–2 times/week	≥3 times/week	P for trend	Rarely	1–3 times/month	1–2 times/week	≥3 times/week	P for trend	
Participants, n	5046	14579	9890	5040		5599	17562	13746	9340		
Person-years	43476	127245	87526	45597		50112	157300	125102	87757		
All causes											
Deaths, n	255	587	469	307		129	264	258	213		
Model 1*	1.00	0.76 (0.65–0.88)	0.76 (0.65–0.89)	0.78 (0.66–0.92)	0.030	1.00	0.64 (0.51–0.79)	0.64 (0.52–0.80)	0.62 (0.50–0.78)	0.003	
Model 2†	1.00	0.79 (0.68–0.91)	0.80 (0.68–0.93)	0.83 (0.70–0.98)	0.128	1.00	0.69 (0.55–0.85)	0.71 (0.57–0.89)	0.69 (0.55–0.86)	0.023	0.238
Model 3‡	1.00	0.81 (0.69–0.94)	0.84 (0.71–0.99)	0.87 (0.73–1.05)	0.391	1.00	0.68 (0.55–0.85)	0.72 (0.57–0.90)	0.69 (0.54–0.88)	0.041	
Model 4§	1.00	0.82 (0.70–0.95)	0.87 (0.73–1.03)	0.95 (0.78–1.17)	0.968	1.00	0.68 (0.54–0.84)	0.72 (0.57–0.91)	0.76 (0.58–1.00)	0.253	
Cancer											
Deaths, n	141	380	286	181		72	169	153	113		
Model 1*	1.00	0.84 (0.69–1.02)	0.80 (0.65–0.98)	0.80 (0.64–1.01)	0.074	1.00	0.70 (0.53–0.92)	0.66 (0.50–0.88)	0.60 (0.44–0.81)	0.004	

Model 2†	1.00	0.86 (0.71–1.05)	0.82 (0.67–1.01)	0.83 (0.66–1.04)	0.130	1.00	0.73 (0.55–0.96)	0.71 (0.53–0.94)	0.63 (0.46–0.86)	0.011	0.167
Model 3‡	1.00	0.86 (0.71–1.05)	0.83 (0.67–1.03)	0.83 (0.66–1.06)	0.161	1.00	0.72 (0.54–0.96)	0.71 (0.53–0.96)	0.64 (0.46–0.89)	0.027	
Model 4§	1.00	0.89 (0.73–1.09)	0.88 (0.70–1.10)	0.90 (0.69–1.18)	0.493	1.00	0.70 (0.53–0.94)	0.70 (0.51–0.95)	0.69 (0.48–0.98)	0.107	
CVD											
Deaths, n	38	67	59	40		20	41	39	36		
Model 1*	1.00	0.62 (0.42–0.93)	0.68 (0.45–1.03)	0.72 (0.46–1.14)	0.374	1.00	0.74 (0.43–1.27)	0.67 (0.39–1.17)	0.68 (0.39–1.19)	0.236	
Model 2†	1.00	0.67 (0.45–1.00)	0.75 (0.50–1.14)	0.82 (0.52–1.30)	0.718	1.00	0.84 (0.49–1.44)	0.80 (0.46–1.39)	0.79 (0.45–1.39)	0.463	0.867
Model 3‡	1.00	0.71 (0.47–1.07)	0.87 (0.56–1.34)	0.97 (0.59–1.59)	0.744	1.00	0.81 (0.46–1.40)	0.78 (0.44–1.37)	0.78 (0.43–1.42)	0.486	
Model 4§	1.00	0.71 (0.47–1.08)	0.89 (0.56–1.40)	1.11 (0.63–1.93)	0.504	1.00	0.76 (0.44–1.33)	0.75 (0.42–1.34)	0.87 (0.45–1.68)	0.785	
Other causes											
Deaths, n	76	140	124	86		37	54	66	64		
Model 1*	1.00	0.66 (0.50–0.88)	0.74 (0.55–0.98)	0.77 (0.56–1.06)	0.387	1.00	0.47 (0.31–0.72)	0.59 (0.39–0.88)	0.64 (0.42–0.97)	0.484	
Model 2†	1.00	0.71 (0.54–0.94)	0.80 (0.60–1.07)	0.85 (0.62–1.16)	0.721	1.00	0.52 (0.34–0.80)	0.69 (0.46–1.04)	0.75 (0.49–1.14)	0.950	0.905
Model 3‡	1.00	0.74	0.87	0.95	0.776	1.00	0.53	0.70	0.75	0.925	

		(0.56–0.99)	(0.65–1.18)	(0.67–1.33			(0.34–0.81)	(0.46–1.08)	(0.47–1.19	
Model 4§	1.00	0.73 (0.55–0.98)	0.87 (0.63–1.19)	1.03 (0.70–1.51	0.588	1.00	0.55 (0.36–0.85)	0.76 (0.48–1.18)	0.87 (0.52–1.44)	0.759

Abbreviations: BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; JDI, Japanese diet index.

*Adjusted for age and study area.

†In males, values are adjusted for covariates in Model 1 plus BMI, smoking habit, alcohol consumption, education level, leisure-time physical activity, and self-reported medical history
  of hypertension, diabetes, and dyslipidemia.
  In females, values are adjusted for covariates in Model 1 plus BMI, smoking habit, alcohol consumption, education level, leisure-time physical activity, self-reported medical history of
  hypertension, diabetes, and dyslipidemia, age at menarche, number of births, and menopausal status.

‡Adjusted for covariates in Model 2 plus total energy intake, energy-adjusted intakes of green and yellow vegetables, light-colored vegetables, fruit, meat, rice, sodium, and dietary fiber,
  and JDI
score.

§Adjusted for covariates in Model 3 plus energy-adjusted intakes of n-3 highly unsaturated fatty acids, calcium, vitamin D, retinol, and carotene.

||Adjusted for sex, age, study area, BMI, smoking habit, alcohol consumption, education level, leisure-time physical activity, self-reported medical history of hypertension, diabetes, and
  dyslipidemia, total energy intake, energy-adjusted intakes of green and yellow vegetables, light-colored vegetables, fruit, meat, rice, sodium, and dietary fiber, JDI score, and cross-
  product term (i.e., sex [dichotomous] × category of small fish consumed [continuous]), representing the interaction.

TABLE 4 Multivariable-adjusted HRs (95% CIs) for all-cause mortality by sex according to the frequency of the intake of small fish in the analysis stratified by age, smoking status, and JDI score*

	Male						Female					
	Rarely	1–3 times/month	1–2 times/week	≥3 times/week	P trend	P for interaction	Rarely	1–3 times/month	1–2 times/week	≥3 times/week	P trend	P for interaction
≥60 years old												
Participants, n	1468	4894	4346	3038			1282	4443	5274	5171		
All-cause deaths, n	159	369	332	247			71	130	168	164		
HR (95% CI)	1.00	0.78	0.82	0.85	0.467		1.00	0.62	0.71	0.69	0.264	
		(0.64–0.94)	(0.67–0.99)	(0.68–1.05)		0.289		(0.46–0.83)	(0.53–0.96)	(0.51–0.94)		0.827
<60 years old												
Participants, n	3578	9685	5544	2002			4317	13119	8472	4169		
All-cause deaths, n	96	218	137	60			58	134	90	49		
HR (95% CI)	1.00	0.88	0.90	0.97	0.835		1.00	0.76	0.70	0.65	0.048	
		(0.69–1.13)	(0.68–1.20)	(0.68–1.38)				(0.55–1.05)	(0.49–0.99)	(0.42–0.99)		
Smoker (former or current)												
Participants, n	3507	10346	6981	3465			1177	2894	1691	874		
All-cause deaths, n	215	468	373	249			20	56	47	23		
HR (95% CI)	1.00	0.75	0.78	0.86	0.375	0.892	1.00	1.21	1.68	1.08	0.515	0.268
		(0.63–0.88)	(0.65–0.93)	(0.70–1.05)				(0.71–2.06)	(0.94–2.99)	(0.55–2.12)		
Never smoker												
Participants, n	1522	4188	2883	1562			4397	14577	11978	8414		
All-cause deaths, n	40	118	96	58			106	207	211	187		
HR (95% CI)	1.00	1.10	1.14	0.91	0.657		1.00	0.60	0.62	0.61	0.011	
		(0.76–1.58)	(0.78–1.68)	(0.59–1.41)				(0.47–0.76)	(0.48–0.79)	(0.47–0.79)		
JDI score ≤3												
Participants, n	3456	8325	3510	906		0.045	3820	9880	4845	1422		0.525
All-cause deaths, n	167	304	140	59			66	125	78	32		

HR (95% CI)	1.00	0.73 (0.60–0.88)	0.68 (0.54–0.86)	0.84 (0.61–1.15)	0.038	1.00	0.76 (0.56–1.04)	0.85 (0.60–1.21)	0.99 (0.63–1.56)	0.971
JDI score ≥4										
Participants, n	1590	6254	6380	4134		1779	7682	8901	7918	
All-cause deaths, n	88	283	329	248		63	139	180	181	
HR (95% CI)	1.00	0.96 (0.75–1.22)	1.03 (0.81–1.31)	0.98 (0.76–1.26)	0.868	1.00	0.61 (0.45–0.83)	0.63 (0.46–0.84)	0.56 (0.41–0.77)	0.008

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio; JDI, Japanese diet index.

*In males, HRs were adjusted for age, study area, BMI, smoking habit, alcohol consumption, education level, leisure-time physical activity, self-reported medical history of hypertension,
   diabetes, and dyslipidemia, total energy intake, energy-adjusted intakes of green and yellow vegetables, light-colored vegetables, fruit, meat, rice, sodium, and dietary fiber, and JDI score.

   In females, HRs were adjusted for the same covariates as in males plus age at menarche, number of births, and menopausal status.

TABLE 5 Multivariable-adjusted HRs (95% CIs) for cancer mortality by sex according to the frequency of the intake of small fish in the analysis stratified by age, smoking status, and JDI score*

	Male						Female					
	Rarely	1–3 times/month	1–2 times/week	≥3 times/week	P for trend	P for interaction	Rarely	1–3 times/month	1–2 times/week	≥3 times/week	P for trend	P for interaction
≥60 years old												
Participants, n	1468	4894	4346	3038			1282	4443	5274	5171		
Cancer deaths, n	85	249	198	144			34	77	95	81		
HR (95% CI)	1.00	0.92	0.86	0.89	0.376		1.00	0.65	0.71	0.61	0.134	
		(0.72–1.19)	(0.66–1.12)	(0.66–1.19)		0.175		(0.43–0.99)	(0.47–1.08)	(0.40–0.95)		0.909
<60 years old												
Participants, n	3578	9685	5544	2002			4317	13119	8472	4169		
Cancer deaths, n	56	131	88	37			38	92	58	32		
HR (95% CI)	1.00	0.82	0.83	0.82	0.454		1.00	0.78	0.64	0.63	0.057	
		(0.59–1.13)	(0.58–1.20)	(0.52–1.30)				(0.53–1.15)	(0.41–1.00)	(0.37–1.08)		
Smoker (former or current)												
Participants, n	3507	10346	6981	3465			1177	2894	1691	874		
Cancer deaths, n	122	303	238	153			10	34	28	16		
HR (95% CI)	1.00	0.78	0.77	0.82	0.264	0.400	1.00	1.40	1.81	1.24	0.555	0.059
		(0.63–0.97)	(0.61–0.98)	(0.63–1.07)				(0.67–2.91)	(0.82–3.99)	(0.51–3.04)		
Never smoker												
Participants, n	1522	4188	2883	1562			4397	14577	11978	8414		
Cancer deaths, n	19	76	48	28			61	135	125	95		
HR (95% CI)	1.00	1.37	1.10	0.81	0.179		1.00	0.62	0.59	0.53	0.003	
		(0.82–2.29)	(0.63–1.91)	(0.43–1.52)				(0.46–0.85)	(0.43–0.82)	(0.37–0.75)		
JDI score ≤3												
Participants, n	3456	8325	3510	906			3820	9880	4845	1422		
Cancer deaths, n	105	201	82	32		0.002	39	86	50	17		0.621
HR (95% CI)	1.00	0.70	0.57	0.60	< 0.001		1.00	0.84	0.83	0.84	0.511	
		(0.55–0.89)	(0.42–0.77)	(0.39–0.91)				(0.57–1.25)	(0.53–1.30)	(0.46–1.54)		

JDI score ≥4

Participants, n	1590	6254	6380	4134		1779	7682	8901	7918	
Cancer deaths, n	36	179	204	149		33	83	103	96	
HR (95% CI)	1.00	1.33	1.34	1.25	0.633	1.00	0.61	0.59	0.52	0.016
		(0.92–1.91)	(0.93–1.92)	(0.86–1.82)			(0.41–0.93)	(0.40–0.89)	(0.34–0.79)	

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio; JDI, Japanese diet index.

*In males, HRs were adjusted for age, study area, BMI, smoking habit, alcohol consumption, education level, leisure-time physical activity, self-reported medical history of hypertension, diabetes, and dyslipidemia, total energy intake, energy-adjusted intakes of green and yellow vegetables, light-colored vegetables, fruit, meat, rice, sodium, and dietary fiber, and JDI score.

In females, HRs were adjusted for the same covariates as in males plus age at menarche, number of births, and menopausal status.