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Original article

Cruciferous vegetable intake and mortality in middle-aged adults: A prospective cohort study

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SUMMARY

Background & aims: Cruciferous vegetables contain isothiocyanates, which effectively reduce inflammation and oxidative stress related to chronic diseases, inhibit the bioactivation of procarcinogens, and enhance the excretion of carcinogens. However, at present, no large cohort studies have investigated the effect of cruciferous vegetable on mortality. We aimed to examine the association between cruciferous vegetable intake and all-cause mortality, namely cancer, heart disease, cerebrovascular disease, and injuries, in a large cohort study conducted between 1990 and 1993, in Japan.
Methods: The analysis included 88,184 participants (age: 45–74 years) with no history of cancer, myocardial infarction, and stroke. Participants were tracked for a median of 16.9 years, during which 15,349 deaths were occurred. The association between cruciferous vegetable intake and risk of all-cause and cause-specific mortality was determined by Cox proportional hazard regression analysis to calculate the hazard ratios (HRs) and 95% confidence intervals (CIs), after adjustment for potential confounding factors.
Results: An inverse association was found between cruciferous vegetable intake and total mortality in both gender. HRs (95% CI) for all-cause mortality in the highest compared to the lowest quintile were 0.86 (0.80, 0.93) for men ($P = 0.0002$ for trend) and 0.89 (0.81, 0.98) for women ($P = 0.03$ for trend). Cruciferous vegetable intake was associated with lower cancer mortality in men, as well as with heart disease-, cerebrovascular disease-, and injury-related mortality in women.
Conclusions: This prospective study suggests that a higher cruciferous vegetables intake is associated with reduced risk of all-cause mortality.

1. Introduction

Cruciferous vegetables, namely cabbage, Chinese radishes, and leaf mustard, are abundant sources of isothiocyanates, which exhibit health benefits [1]. Isothiocyanates are synthetized from glucosinolates when the tissue of cruciferous vegetables is destroyed during food preparation or chewing by the action of an enzyme called myrosinase [1]. Although the mechanisms underlying isothiocyanates' protective properties against chronic

Abbreviations: FFQ, food frequency questionnaire; HR, hazard ratio; CI, confidence interval; JPHC, The Japan Public Health Center-based; PHC, public health center.

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diseases are not well documented, isothiocyanates have been reported to supress inflammation and oxidative stress [2–4], which are closely linked with chronic diseases. Isothiocyanates have been reported to inhibit the bioactivation of procarcinogens and potentially enhance the excretion of carcinogens before they damage the DNA, thus possibly leading to cancer prevention [5,6]. Along with cancer prevention, cruciferous vegetables may contribute to survival in certain cancers [7,8]. In addition to isothiocyanates, cruciferous vegetables contain several micronutrients, including folate, vitamin C, tocopherols, and carotenoids [9], that are associated with reduced risk of mortality [10].

Compared with the intake of cruciferous vegetables in Western populations (approximately 22.6 g/d) [11], intakes in Asian populations exceed 60 g/d [12,13]. Asian populations also have the longest life expectancy, particularly those residing in Japan [14] and Hong Kong [15]. Therefore, the longer life expectancy in Japan may be attributed to cruciferous vegetable intake. Two prospective studies have examined the association between cruciferous vegetable intake and mortality; however, these studies were limited to all-cause, cancer, and cardiovascular disease mortality [16,17], and the findings were inconclusive. In addition, a few have reported that cruciferous vegetable intake was linked with less cognitive decline [18,19].

To date, subgroup analyses addressing the effect of smoking status or specific cruciferous vegetable intake on mortality have not been conducted. Individual cruciferous species were reported to contain different precursors of glucosinolate [20], which when catalysed into isothiocyanates, may exert unique effects on mortality risk. Because the dose–response trend of individual cruciferae species has not been investigated, this association requires further elucidation. Thus, the present study aimed to comprehensively investigate the association between cruciferous vegetable intake with total mortality and the five leading causes of death among Japanese middle-aged men and women [21].

2. Materials and methods

2.1. Study population

The Japan Public Health Center-based prospective (JPHC) study is a continuous population-based cohort study conducted between 1990 and 1993 that represents registered local residents living in the area of 11 public health center (PHCs) in Japan. At study recruitment, participants were aged 40–69 years. The study design has been described previously [22]. The study was approved by the Institutional Review Board of the National Cancer Center, Tokyo, Japan.

In this large prospective study, the 5-year follow-up survey was set as the starting point because more comprehensive questions on dietary behaviour were included in this survey than in the baseline survey. The 5-year follow-up questionnaire additionally required information on demographics, medical history, and smoking status. Of the potential 137,593 participants, 101,230 participants completed the questionnaire (response rate = 73.6%). Participants were excluded if they had been diagnosed with cancer ($n = 3020$), myocardial infarction ($n = 2602$), and stroke ($n = 1076$) before the follow-up survey. Participants were also excluded if they did not answer the question on the frequency of cruciferous vegetable intake ($n = 1709$) and if they reported a daily energy intake that was 2.5% more or less than the established range (1025–4220 kcal for men and 867–3688 kcal for women; $n = 4639$). Finally, 88,184 participants (40,662 men and 47,562 women) were included in the analysis.

2.2. Dietary assessment

The Food Frequency Questionnaire (FFQ) distributed at the 5-year follow-up survey was used to collect information on habitual dietary intake of 138 items (including eight cruciferous vegetables and three pickled cruciferous vegetables) in the previous year according to nine frequency categories. Portion sizes of each food item was reported as small (50% less than the standard serving size), medium (proportional to the standard serving size), and large (50% larger than the standard serving size). The nine frequency categories were reported as: never, 1–3 times/mo, 1–2 times/wk, 3–4 times/wk, 5–6 times/wk, once/d, 2–3 times/d, 4–6 times/d, and ≥7 times/d. Eleven cruciferous vegetables (including three pickled cruciferous vegetables) were categorized as 'cruciferous vegetables', according to the grouping rules adopted in the *International Agency for Research on Cancer Handbook of Cancer Prevention Volume 9: Cruciferous vegetables, isothiocyanate and indoles* [13]. The frequency of intake was multiplied by the standard and relative portion sizes to derive the dietary intake of each food item. All food intake was log-transformed and energy-adjusted by using the residual method [23]. The FFQ's validity for the assessment of cruciferous vegetable intake was previously examined, and the reproducibility of the intake was validated through the administration of the FFQ after 1-year interval. Spearman's correlation coefficients between energy-adjusted intake derived from the FFQ and 28-day (or 14-day for the Okinawa PHC area) dietary records for men and women were 0.31 and 0.34, respectively [24].

2.3. Follow-up

All subjects enrolled in the 5-year follow-up survey were monitored through December 31, 2014, or till their death. Exceptions were applied to the Tokyo and Osaka PHC areas, for which the follow-up was concluded on December 31, 2009, and December 31, 2012, respectively. Participants who have died or relocated to other municipalities were specified on an annual basis through residential records in each PHC area. Each case of death was confirmed by the mortality table from the Ministry of Health, Labour and Welfare. Of all study participants, 35 (0.04%) moved out of Japan, and were unable to track 300 (0.3%) during the study period. Within the period of 1,433,844 person-years (median follow-up time: 16.9 years), 15,349 (9588 men and 5761 women) deaths were reported.

The cause of death was assigned according to the *International Classification of Diseases and Related Health Problems, 10th revision* [25]. We included mortality from all-causes, cancer (C00–C97); heart disease (I20–I99); cerebrovascular disease (I60–I69); respiratory disease (J10–J18 and J40–J47), including pneumonia, influenza, chronic obstructive pulmonary disease and associated conditions; injuries and accidents (V01–X59, X60–X84, X85–Y09, and Y85–Y86); and other remaining causes, as the endpoint for the present study.

2.4. Statistical analysis

We calculated the person-years of follow-up for each subject from the 5-year follow-up survey completion until the date of death, relocation, or follow-up completion, whichever occurred first.

The Cox proportional hazard model was used to estimate the hazard ratios (HRs) and 95% confidence internals (95% CIs) of the total and cause-specific mortality according to the quintile of cruciferous vegetable intake, by adjusting for potential covariates. The lowest quintile of cruciferous vegetable intake was used as a reference. *P* values for linear trends were computed by assigning ordinal variables for quintiles of cruciferous vegetables intake and adding the number as a continuous variable into the model.

2.5. Age- and area adjusted and multivariate model

The basic model was adjusted only for age (continuous) and study area (11 PHC area categories). The multivariable adjusted model was additionally adjusted for the body mass index (BMI) (<18.5, 18.5–25, 25–30, or >30 kg/m^2), smoking status, and number of cigarettes smoked (never; past; current: <10, 10–19, 20–29, 30–39, or ≥40 cigarettes/d for men and <20 or ≥20 cigarettes/d for women), drinking status and amount of alcohol consumption (non-drinker; current drinker: 1–150, 151–300, 301–450, or ≥451 g ethanol/wk for men and non-drinker and current drinker for women), physical activity (metabolic equivalent, task h/d; continuous), history of hypertension (yes or no), history of diabetes (yes or no), frequency of coffee consumption (almost never and <1, 1, or ≤2 cups/d), frequency of green tea consumption (almost never and <1, 1, 2–3, or ≤4 cups/d), energy intake (continuous), salt intake (quintile), non-cruciferous vegetable intake (quintile), fruit intake (quintile), occupational category (agriculture/forestry/fishery, salaried/professional, self-employed, housework/unemployed, or other), and screening examination (yes or no).

2.6. Sensitivity analysis

In addition, we conducted sensitivity analyses after excluding 2532 participants who died in the first 5 years of follow-up, to avoid the potential influence of subclinical illnesses in participants that might have modified their diet.

2.7. Subgroup analysis

Subgroup analysis according to age, smoking, and drinking status was performed to determine the association between cruciferous vegetable intake and mortality risk. Cox proportional hazard regression analysis was repeated to calculate the HRs and 95% CIs for each subgroup analysis.

2.8. Analysis on specific cruciferous vegetables

The analysis was then repeated to assess the association between specific cruciferous vegetable intake and total mortality to identify individual contribution to longevity. Multivariable HRs and 95% CIs before and after exclusion of deaths reported in the first 5-year of follow-up were computed using Cox proportional hazard regression model.

In the models, Schoenfeld residuals were used to test the proportional hazard assumption by including a product term between a fifth of the cruciferous vegetable intake and follow-up, but no correlation was detected. The reported P values were two-sided, and $P < 0.05$ was considered statistically significant. All analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

3. Results

The characteristics of participants at the baseline according to cruciferous vegetables intake are shown in Table 1. Participants who consumed more cruciferous vegetables were significantly older ($P < 0.0001$), less likely to be current smokers ($P < 0.0001$), and more likely to consume more fruit and vegetables ($P < 0.0001$); however, irrespective of sex, these participants had significantly higher prevalence of hypertension and diabetes ($P < 0.0001$).

A total of 15,349 deaths were reported during the follow-up period, with 5995 deaths caused by cancer, 1968 by heart disease, 1470 by cerebrovascular disease, 1126 by respiratory disease, 1082 by injuries, and 3708 by other causes.

The association between cruciferous vegetable intake and all-cause and cause-specific mortality are described in Table 2 (men) and Table 3 (women). In men, multivariable adjusted HRs were 0.86 (95% CI: 0.80, 0.93; $P = 0.0002$ for trend) in the fifth quintile compared with the first quintile for all-cause mortality. The multivariable model also indicated that cruciferous vegetable intake was significantly inversely associated with cancer mortality in men with HRs of 0.84 (95% CI: 0.75, 0.96; $P = 0.001$ for trend). No association was found between cruciferous vegetable intake and mortality from other causes (Table 2 and Fig. 1).

For women, the multivariable model showed a significantly inverse association between cruciferous vegetable intake and heart disease mortality (HR: 0.73; 95% CI: 0.57, 0.95; $P = 0.01$ for trend) and cerebrovascular disease mortality (HR: 0.78; 95% CI: 0.58, 1.05; $P = 0.05$ for trend). In addition, a significant inverse association was observed between cruciferous vegetable intake and injury-related mortality (HR: 0.60; 95% CI: 0.39, 0.90; $P = 0.005$ for trend; Table 3). The results were essentially unchanged after excluding cases of deaths identified during the first 5 years of follow-up. No association was detected between cruciferous vegetable intake and mortality from cancer and other causes (Fig. 2).

To consider the potential effect of age on the association between cruciferous vegetable intake and mortality as well as the cause-specific mortality, we conducted subgroup analyses by age, smoking and drinking status. Stratification by age categories did not change the results substantially in both gender. In men, inverse association was observed between cruciferous vegetable intake and mortality in all age categories (HR: 0.79; 95% CI: 0.60, 1.04; $P = 0.11$ for <50 years, HR: 0.86; 95% CI: 0.74, 1.00; $P = 0.03$ for 50 to <60 years, HR: 0.88; 95% CI: 0.79, 0.97; $P = 0.01$ for ≥60 years). The age category did not show an impact on the association between cruciferous vegetable intake and mortality in women (HR: 0.83; 95% CI: 0.56, 1.23; $P = 0.42$ for <50 years, HR: 0.85; 95% CI: 0.69, 1.05; $P = 0.16$ for 50 to <60 years, HR: 0.90; 95% CI: 0.80, 1.02; $P = 0.09$ for ≥60 years).

The results of the subgroup analysis by the smoking status for men (never smoked and always smoked) and women (never smoked) are shown in Table 4 and Supplemental Table 1, respectively. In men, an inverse association was found between cruciferous vegetable intake and all-cause mortality, regardless of the smoking status. An inverse association was also observed between cruciferous vegetable intake and cancer mortality among men who smoked. In women, a significant inverse association was observed between cruciferous vegetable intake and all-cause, heart disease-, and injury-related mortality in those who never smoked.

Furthermore, subgroup analyses are also shown for men who were categorised as non-drinkers, moderate drinkers (<300 g ethanol/wk), and heavy drinkers (≥300 g ethanol/wk); and women who were non-drinkers (Table 5 and Supplemental Table 2, respectively). In men, we observed a significant inverse association between cruciferous vegetable intake and all-cause mortality among moderate and heavy drinkers. The observed associations are primarily from cancer and heart disease mortality. We then additionally conducted an analysis to assess the association between cruciferous vegetable intake and cancer mortality stratified by combining both smoking and drinking status; the result showed that among non-smokers and heavy drinkers, cruciferous vegetable intake was associated significantly with cancer mortality in men (HR: 0.53; 95% CI: 0.31, 0.91; $P = 0.003$ for trend). In women, we observed a significant inverse association between cruciferous vegetable intake and all-cause, heart disease-, and cerebrovascular disease-mortality among non-drinkers.

Table 1
Baseline characteristics of participants according to quintile of cruciferous vegetable intake (n = 88,184)[a].

	Men (n = 40,622)					*P*-value[b]	Women (n = 47,562)					*P*-value[b]
	Quintile of CV intake						Quintile of CV intake					
	Lowest (Q1)	Second (Q2)	Third (Q3)	Fourth (Q4)	Highest (Q5)		Lowest (Q1)	Second (Q2)	Third (Q3)	Fourth (Q4)	Highest (Q5)	
No. of participants	8124	8125	8124	8125	8124	–	9512	9513	9512	9513	9512	–
Age	54.7 ± 7.5	55.2 ± 7.5	55.9 ± 7.5	56.9 ± 7.7	58.4 ± 7.8	<0.0001	55.6 ± 8.0	55.8 ± 7.7	56.4 ± 7.7	57.1 ± 7.7	58.1 ± 7.7	<0.0001
Body mass index	23.6 ± 3.0	23.6 ± 2.9	23.5 ± 2.8	23.6 ± 2.8	23.6 ± 2.8	0.37	23.4 ± 3.3	23.4 ± 3.1	23.4 ± 3.1	23.5 ± 3.1	23.6 ± 3.2	<0.0001
Current smoker (%)	51.8	48.9	47.4	44.8	43.0	<0.0001	7.8	6.1	5.5	4.9	4.5	<0.0001
Current drinker (%)	79.7	79.2	78.0	75.3	70.5	<0.0001	23.2	22.6	21.3	19.5	16.4	<0.0001
History of hypertension (%)	12.3	13.0	13.9	15.3	16.3	<0.0001	11.1	12.8	13.4	13.7	15.2	<0.0001
History of diabetes (%)	7.5	7.7	8.2	8.3	10.5	<0.0001	3.5	3.3	3.7	3.9	5.7	<0.0001
Physical activity (metabolic equivalent, task h/d)	31.9 ± 6.9	32.4 ± 6.9	32.7 ± 7.0	32.7 ± 7.0	32.8 ± 7.1	<0.0001	31.0 ± 6.0	31.6 ± 5.9	31.7 ± 5.9	32.0 ± 6.0	32.0 ± 6.1	<0.0001
Screening examination (%)	77.2	81.8	83.0	84.6	85.1	<0.0001	79.5	83.8	85.3	86.3	87.2	<0.0001
Coffee > 1 time/d (%)	35.0	36.4	34.6	32.6	28.6	<0.0001	43.6	40.6	38.8	34.6	28.0	<0.0001
Green tea > 1 time/d (%)	47.7	54.3	58.8	62.1	66.1	<0.0001	52.5	59.3	62.6	64.2	68.8	<0.0001
Dietary intake[c]												
Energy (kcal/d)	2147 ± 668	2191 ± 646	2214 ± 629	2187 ± 613	2115 ± 630	0.003	1844 ± 601	1885 ± 568	1898 ± 545	1852 ± 525	1818 ± 555	<0.0001
Dietary fibre (g/d)	8.2 ± 4.4	10.3 ± 4.6	11.9 ± 5.1	13.5 ± 5.5	16.5 ± 7.5	<0.0001	10.2 ± 5.1	12.4 ± 5.4	14.0 ± 5.8	15.1 ± 6.2	18.1 ± 8.1	<0.0001
Salt (g/d)	9.7 ± 4.8	11.5 ± 5.1	12.6 ± 5.3	13.4 ± 5.5	15.3 ± 6.6	<0.0001	9.7 ± 4.7	11.3 ± 16.9	12.2 ± 17.1	12.7 ± 5.3	14.8 ± 6.6	<0.0001
Total CV (g/d)[d]	22 ± 8	43 ± 5	63 ± 6	88 ± 9	163 ± 68	–	29 ± 10	54 ± 6	75 ± 7	103 ± 10	183 ± 73	–
Cabbage (g/d)	5 ± 4	10 ± 6	13 ± 8	17 ± 10	28 ± 28	<0.0001	6 ± 5	12 ± 8	15 ± 9	19 ± 12	30 ± 30	<0.0001
Chinese radish (g/d)	6 ± 5	13 ± 7	20 ± 10	28 ± 14	51 ± 45	<0.0001	8 ± 6	16 ± 9	24 ± 12	32 ± 16	57 ± 52	<0.0001
Pickled Chinese radish (g/d)	2 ± 3	4 ± 5	6 ± 8	9 ± 13	19 ± 25	<0.0001	2 ± 4	5 ± 7	7 ± 10	12 ± 15	22 ± 28	<0.0001
Pickled rape and leaf mustard (g/d)	1 ± 2	3 ± 4	4 ± 6	7 ± 9	14 ± 22	<0.0001	2 ± 3	3 ± 5	5 ± 7	7 ± 11	16 ± 24	<0.0001
Pickled Chinese leaves (g/d)	2 ± 2	4 ± 4	5 ± 5	7 ± 8	14 ± 18	<0.0001	2 ± 3	4 ± 4	5 ± 6	8 ± 9	16 ± 19	<0.0001
Komatsuna (g/d)	0.5 ± 0.9	0.8 ± 1.5	1.2 ± 1.9	1.7 ± 2.6	2.7 ± 5.0	<0.0001	0.8 ± 1.4	1.4 ± 2.1	1.8 ± 2.8	2.4 ± 3.6	3.6 ± 6.5	<0.0001
Broccoli (g/d)	1 ± 2	2 ± 3	3 ± 4	4 ± 5	6 ± 9	<0.0001	2 ± 3	4 ± 4	5 ± 5	6 ± 6	8 ± 11	<0.0001
Chinese leaves (g/d)	1 ± 2	4 ± 4	6 ± 5	8 ± 7	14 ± 16	<0.0001	3 ± 3	5 ± 4	7 ± 5	9 ± 8	15 ± 16	<0.0001
Pak choi (g/d)	1 ± 2	2 ± 3	2 ± 4	4 ± 6	6 ± 13	<0.0001	2 ± 2	3 ± 4	4 ± 5	5 ± 7	8 ± 14	<0.0001
Leaf mustard (g/d)	0.6 ± 1.7	1.1 ± 2.6	1.6 ± 3.9	2.2 ± 4.9	4.8 ± 15.2	<0.0001	0.9 ± 2.1	1.4 ± 3.2	1.8 ± 4.3	2.5 ± 5.9	4.7 ± 13.5	<0.0001
Swiss chard (g/d)	0.3 ± 1.2	0.4 ± 1.8	0.7 ± 3.1	1.0 ± 4.5	2.7 ± 13.8	<0.0001	0.4 ± 1.7	0.6 ± 2.5	0.8 ± 3.6	1.3 ± 5.2	2.8 ± 14.3	<0.0001
Other vegetables (g/d)	67 ± 59	90 ± 63	108 ± 63	131 ± 69	180 ± 107	<0.0001	88 ± 69	109 ± 64	128 ± 69	148 ± 72	196 ± 105	<0.0001
Fruit (g/d)	120 ± 129	149 ± 124	167 ± 132	190 ± 142	222 ± 165	<0.0001	184 ± 162	214 ± 150	233 ± 155	251 ± 155	279 ± 183	<0.0001
Employed (%)	90.9	91.7	91.0	90.0	88.0	<0.0001	57.1	54.9	52.2	50.3	48.2	<0.0001

Abbreviations: CV, cruciferous vegetables; SD, standard deviation.
[a] Values are mean ± SD unless stated otherwise.
[b] Determined by using chi-squared for categorical variables or ANOVA test for continuous variables.
[c] All dietary intake are energy adjusted by residual method.
[d] Cruciferous vegetables include cabbage, Chinese radish, pickled Chinese radish, pickled rape and leaf mustard, and pickled Chinese leaves, *komatsuna*, broccoli, Chinese leaves, pak choi, leaf mustard, and Swiss chard.

Table 2
Multivariable adjusted hazard ratios of all-cause mortality and cause-specific mortality according to cruciferous vegetable intake among men.[a]

	Quintile of CV intake					P for trend
	Lowest	Second	Third	Fourth	Highest	
Men (n = 40,642)						
All-cause mortality						
No. of cases (n = 9588)	1817	1725	1864	1950	2232	–
Person-years (n = 641,646)	126,486	128,534	128,513	129,728	128,385	–
Crude HR	1.00 (reference)	0.93 (0.87, 0.99)	1.00 (0.94, 1.07)	1.03 (0.97, 1.10)	1.20 (1.12, 1.27)	<0.0001
Age- and area-adjusted HR	1.00 (reference)	0.87 (0.82, 0.93)	0.89 (0.83, 0.95)	0.83 (0.78, 0.88)	0.83 (0.78, 0.88)	<0.0001
Multivariable adjusted HR[b]	1.00 (reference)	0.94 (0.87, 1.00)	0.96 (0.90, 1.03)	0.89 (0.83, 0.96)	0.86 (0.80, 0.93)	0.0002
Excluding first 5 years (n = 38,920)						
No. of cases (n = 7886)	1480	1421	1524	1611	1850	–
Multivariable adjusted HR[c]	1.00 (reference)	0.95 (0.88, 1.02)	0.98 (0.90, 1.05)	0.92 (0.85, 0.99)	0.90 (0.82, 0.98)	0.02
Cancer						
No. of cases (n = 3881)	717	713	798	747	906	–
Crude HR	1.00 (reference)	0.97 (0.88, 1.08)	1.09 (0.98, 1.20)	1.00 (0.91, 1.11)	1.23 (1.12, 1.36)	<0.0001
Age- and area-adjusted HR	1.00 (reference)	0.92 (0.83, 1.02)	0.97 (0.87, 1.07)	0.81 (0.73, 0.89)	0.86 (0.78, 0.95)	0.0003
Multivariable adjusted HR[b]	1.00 (reference)	0.93 (0.84, 1.04)	0.98 (0.88, 1.09)	0.81 (0.72, 0.91)	0.84 (0.75, 0.96)	0.001
Excluding first 5 years						
No. of cases (n = 3109)	574	571	637	597	730	–
Multivariable adjusted HR[c]	1.00 (reference)	0.94 (0.83, 1.06)	0.99 (0.88, 1.12)	0.83 (0.72, 0.94)	0.89 (0.77, 1.02)	0.02
Heart disease						
No. of cases (n = 1192)	229	199	219	279	266	–
Crude HR	1.00 (reference)	0.85 (0.70, 1.03)	0.93 (0.77, 1.12)	1.17 (0.98, 1.39)	1.13 (0.95, 1.35)	0.005
Age- and area-adjusted HR	1.00 (reference)	0.80 (0.66, 0.97)	0.84 (0.70, 1.01)	0.95 (0.79, 1.13)	0.79 (0.66, 0.95)	0.16
Multivariable adjusted HR[b]	1.00 (reference)	0.86 (0.71, 1.05)	0.91 (0.75, 1.11)	1.03 (0.84, 1.26)	0.83 (0.67, 1.04)	0.50
Excluding first 5 years						
No. of cases (n = 989)	182	174	174	235	224	–
Multivariable adjusted HR[c]	1.00 (reference)	0.94 (0.76, 1.17)	0.91 (0.73, 1.14)	1.09 (0.87, 1.36)	0.89 (0.70, 1.14)	0.82
Cerebrovascular disease						
No. of cases (n = 856)	160	137	177	176	206	–
Crude HR	1.00 (reference)	0.84 (0.67, 1.05)	1.08 (0.87, 1.34)	1.06 (0.86, 1.31)	1.26 (1.02, 1.54)	0.004
Age- and area-adjusted HR	1.00 (reference)	0.78 (0.62, 0.98)	0.93 (0.75, 1.15)	0.82 (0.66, 1.01)	0.83 (0.67, 1.02)	0.18
Multivariable adjusted HR[b]	1.00 (reference)	0.86 (0.68, 1.09)	1.05 (0.83, 1.33)	0.92 (0.72, 1.17)	0.89 (0.68, 1.16)	0.57
Excluding first 5 years						
No. of cases (n = 710)	132	111	146	151	170	–
Multivariable adjusted HR[c]	1.00 (reference)	0.85 (0.66, 1.11)	1.07 (0.83, 1.39)	0.99 (0.75, 1.29)	0.94 (0.70, 1.25)	1.00
Respiratory disease						
No. of cases (n = 765)	133	134	123	171	204	–
Crude HR	1.00 (reference)	0.98 (0.77, 1.25)	0.90 (0.70, 1.14)	1.22 (0.97, 1.53)	1.48 (1.19, 1.84)	<0.0001
Age- and area-adjusted HR	1.00 (reference)	0.91 (0.72, 1.16)	0.79 (0.61, 1.01)	0.93 (0.74, 1.17)	0.94 (0.75, 1.17)	0.80
Multivariable adjusted HR[b]	1.00 (reference)	1.08 (0.84, 1.38)	0.96 (0.73, 1.25)	1.15 (0.89, 1.50)	1.10 (0.84, 1.46)	0.41
Excluding first 5 years						
No. of cases (n = 691)	120	123	107	155	186	–
Multivariable adjusted HR[c]	1.00 (reference)	1.09 (0.84, 1.42)	0.91 (0.69, 1.21)	1.14 (0.87, 1.50)	1.09 (0.81, 1.46)	0.50
Injury						
No. of cases (n = 740)	152	169	146	134	139	–
Crude HR	1.00 (reference)	1.09 (0.87, 1.35)	0.94 (0.75, 1.18)	0.85 (0.68, 1.08)	0.89 (0.71, 1.12)	0.07
Age- and area-adjusted HR	1.00 (reference)	1.06 (0.85, 1.32)	0.88 (0.70, 1.11)	0.76 (0.60, 0.96)	0.74 (0.58, 0.94)	0.0005
Multivariable adjusted HR[b]	1.00 (reference)	1.16 (0.92, 1.45)	1.01 (0.79, 1.29)	0.91 (0.70, 1.19)	0.87 (0.65, 1.16)	0.12
Excluding first 5 years						
No. of cases (n = 523)	110	115	114	90	94	–
Multivariable adjusted HR[c]	1.00 (reference)	1.06 (0.81, 1.40)	1.06 (0.80, 1.42)	0.82 (0.60, 1.13)	0.80 (0.56, 1.13)	0.09
Other causes						
No. of cases (n = 2154)	426	373	401	443	511	–
Crude HR	1.00 (reference)	0.85 (0.74, 0.98)	0.91 (0.80, 1.05)	0.99 (0.87, 1.13)	1.16 (1.02, 1.32)	0.002
Age- and area-adjusted HR	1.00 (reference)	0.81 (0.70, 0.93)	0.82 (0.71, 0.94)	0.79 (0.69, 0.91)	0.79 (0.69, 0.90)	0.002
Multivariable adjusted HR[b]	1.00 (reference)	0.90 (0.78, 1.04)	0.92 (0.79, 1.07)	0.89 (0.76, 1.03)	0.82 (0.70, 0.97)	0.04
Excluding first 5 years						
No. of cases (n = 1864)	362	327	346	383	446	–
Multivariable adjusted HR[c]	1.00 (reference)	0.92 (0.79, 1.08)	0.94 (0.80, 1.11)	0.92 (0.78, 1.08)	0.87 (0.73, 1.04)	0.17

Abbreviations: CV, cruciferous vegetables; HR, hazard ratio; CI, confidence interval.
[a] A Cox regression model was used to estimate HRs and 95% CIs.
[b] Adjusted for age (continuous), study area (10 PHC area categories), BMI (<18.5, 18.5–25, 25–30, or >30), smoking status (never; past; current: <10, 10–19, 20–29, 30–39, or ≥40 cigarettes/d), alcohol consumption (non-drinker and current drinker: 1–150, 151–300, 301–450 or ≥451 g ethanol/wk), physical activity (metabolic equivalent, task h/d; continuous), history of hypertension (yes or no), history of diabetes (yes or no), coffee consumption (almost never and <1, 1, or ≤2 cups/d), green tea consumption (almost never and <1, 1, 2–3, or ≤4 cups/d), energy intake (continuous), intake of salt (quintile), non-CV (quintile), fruit (quintile), occupation (agriculture/forestry/fishery, salaried/professional, self-employed, housework/unemployed, or other), and screening examination (yes or no).
[c] Analysed after the exclusion of participants who died in the first 5-year follow-up.

Table 6 shows the association between specific cruciferous vegetable intake and all-cause mortality. In men, the highest tertile of broccoli and pickled Chinese radish showed significant inverse associations with all-cause mortality. Women also showed a similar association; the highest tertile of Chinese radish and broccoli showed significant inverse associations with all-cause mortality. Because of an extremely low intake of Swiss chard, individual analyses could not be conducted. The results were virtually

Table 3
Multivariable adjusted hazard ratios of all-cause and cause-specific mortality according to cruciferous vegetable intake among women.[a]

	Quintile of CV intake					*P*-trend
	Lowest	Second	Third	Fourth	Highest	
Women (n = 47,562)						
All-cause mortality						
No. of cases (n = 5761)	1161	1057	1060	1157	1326	–
Person-years (n = 792,198)	154,340	156,959	159,146	160,136	161,616	–
Crude HR	1.00 (reference)	0.89 (0.82, 0.97)	0.87 (0.80, 0.95)	0.94 (0.87, 1.02)	1.06 (0.98, 1.15)	0.04
Age- and area-adjusted HR	1.00 (reference)	0.88 (0.81, 0.95)	0.82 (0.75, 0.89)	0.82 (0.76, 0.90)	0.84 (0.78, 0.91)	<0.0001
Multivariable adjusted HR[b]	1.00 (reference)	0.93 (0.85, 1.01)	0.88 (0.81, 0.96)	0.90 (0.82, 0.98)	0.89 (0.81, 0.98)	0.03
Excluding first 5 years (n = 46,732)[c]						
No. of cases (n = 4931)	969	907	915	1001	1139	–
Multivariable adjusted HR[b]	1.00 (reference)	0.94 (0.86, 1.03)	0.90 (0.82, 0.99)	0.92 (0.83, 1.01)	0.91 (0.82, 1.01)	0.10
Cancer						
No. of cases (n = 2114)	378	382	411	456	487	–
Crude HR	1.00 (reference)	0.99 (0.86, 1.14)	1.04 (0.91, 1.20)	1.15 (1.00, 1.31)	1.21 (1.06, 1.38)	0.0006
Age- and area-adjusted HR	1.00 (reference)	0.97 (0.84, 1.12)	0.99 (0.86, 1.14)	1.03 (0.90, 1.19)	1.02 (0.89, 1.17)	0.55
Multivariable adjusted HR[b]	1.00 (reference)	1.02 (0.88, 1.18)	1.05 (0.91, 1.22)	1.12 (0.96, 1.31)	1.10 (0.93, 1.30)	0.14
Excluding first 5 years[c]						
No. of cases (n = 1737)	300	310	352	377	398	–
Multivariable adjusted HR[b]	1.00 (reference)	1.03 (0.88, 1.21)	1.13 (0.96, 1.34)	1.17 (0.99, 1.39)	1.15 (0.96, 1.38)	0.06
Heart disease						
No. of cases (n = 776)	178	142	128	145	183	–
Crude HR	1.00 (reference)	0.78 (0.62, 0.97)	0.68 (0.54, 0.86)	0.76 (0.61, 0.95)	0.94 (0.77, 1.16)	0.62
Age- and area-adjusted HR	1.00 (reference)	0.78 (0.63, 0.97)	0.64 (0.51, 0.81)	0.66 (0.53, 0.83)	0.72 (0.59, 0.89)	0.002
Multivariable adjusted HR[b]	1.00 (reference)	0.80 (0.64, 1.00)	0.68 (0.53, 0.86)	0.70 (0.55, 0.89)	0.73 (0.57, 0.95)	0.01
Excluding first 5 years[c]						
No. of cases (n = 686)	153	131	119	130	153	–
Multivariable adjusted HR[b]	1.00 (reference)	0.84 (0.66, 1.07)	0.72 (0.56, 0.93)	0.71 (0.55, 0.92)	0.72 (0.54, 0.94)	0.01
Cerebrovascular disease						
No. of cases (n = 614)	122	114	120	116	142	–
Crude HR	1.00 (reference)	0.91 (0.71, 1.18)	0.94 (0.73, 1.21)	0.90 (0.70, 1.16)	1.08 (0.85, 1.38)	0.58
Age- and area-adjusted HR	1.00 (reference)	0.87 (0.67, 1.13)	0.84 (0.65, 1.08)	0.75 (0.58, 0.97)	0.82 (0.64, 1.04)	0.06
Multivariable adjusted HR[b]	1.00 (reference)	0.91 (0.70, 1.19)	0.89 (0.68, 1.17)	0.79 (0.60, 1.05)	0.78 (0.58, 1.05)	0.05
Excluding first 5 years[c]						
No. of cases (n = 510)	104	92	96	96	122	–
Multivariable adjusted HR[b]	1.00 (reference)	0.86 (0.64, 1.15)	0.82 (0.61, 1.11)	0.75 (0.55, 1.03)	0.77 (0.56, 1.07)	0.10
Respiratory disease						
No. of cases (n = 361)	73	70	66	66	86	–
Age- and area-adjusted HR	1.00 (reference)	0.96 (0.69, 1.33)	0.83 (0.60, 1.16)	0.77 (0.55, 1.08)	0.88 (0.64, 1.21)	0.23
Crude HR	1.00 (reference)	0.93 (0.67, 1.30)	0.86 (0.62, 1.20)	0.85 (0.61, 1.18)	1.08 (0.79, 1.48)	0.79
Multivariable adjusted HR[b]	1.00 (reference)	1.01 (0.72, 1.41)	0.90 (0.63, 1.29)	0.83 (0.58, 1.21)	0.95 (0.65, 1.39)	0.53
Excluding first 5 years[c]						
No. of cases (n = 332)	66	65	62	62	77	–
Multivariable adjusted HR[b]	1.00 (reference)	1.02 (0.71, 1.46)	0.92 (0.64, 1.34)	0.85 (0.58, 1.25)	0.92 (0.62, 1.38)	0.48
Injury						
No. of cases (n = 342)	80	77	52	66	67	–
Crude HR	1.00 (reference)	0.99 (0.86, 1.14)	1.05 (0.91, 1.20)	1.15 (1.00, 1.32)	1.21 (1.06, 1.39)	0.0005
Age- and area-adjusted HR	1.00 (reference)	0.87 (0.64, 1.19)	0.55 (0.39, 0.78)	0.65 (0.47, 0.90)	0.61 (0.43, 0.84)	0.0007
Multivariable adjusted HR[b]	1.00 (reference)	0.96 (0.70, 1.33)	0.61 (0.42, 0.88)	0.70 (0.48, 1.02)	0.60 (0.39, 0.90)	0.005
Excluding first 5 years[c]						
No. of cases (n = 268)	59	64	34	53	58	–
Multivariable adjusted HR[b]	1.00 (reference)	1.04 (0.72, 1.50)	0.50 (0.32, 0.78)	0.69 (0.45, 1.05)	0.61 (0.39, 0.97)	0.01
Other causes						
No. of cases (n = 1554)	330	272	283	308	361	–
Crude HR	1.00 (reference)	0.80 (0.68, 0.94)	0.81 (0.69, 0.95)	0.87 (0.75, 1.02)	1.00 (0.86, 1.16)	0.58
Age- and area-adjusted HR	1.00 (reference)	0.81 (0.69, 0.95)	0.77 (0.66, 0.90)	0.77 (0.65, 0.90)	0.78 (0.67, 0.91)	0.0003
Multivariable adjusted HR[b]	1.00 (reference)	0.85 (0.72, 1.01)	0.85 (0.72, 1.01)	0.84 (0.71, 1.00)	0.84 (0.70, 1.01)	0.10
Excluding first 5 years[c]						
No. of cases (n = 1398)	287	245	252	283	331	–
Multivariable adjusted HR[b]	1.00 (reference)	0.88 (0.74, 1.05)	0.87 (0.73, 1.04)	0.89 (0.74, 1.07)	0.89 (0.73, 1.08)	0.32

Abbreviations: CV, cruciferous vegetables; HR, hazard ratio; CI, confidence interval.
[a] A Cox regression model was used to estimate HRs and 95% CIs.
[b] Adjusted for age (continuous), study area (10 PHC area categories), BMI (<18.5, 18.5–25, 25–30, or >30), smoking status (never; past; current: <10, 10–19, 20–29, 30–39, or ≥40 cigarettes/d), alcohol consumption (non-drinker; current drinker: 1–150, 151–300, 301–450 or ≥451 g ethanol/wk), physical activity (metabolic equivalent, task h/d; continuous), history of hypertension (yes or no), history of diabetes (yes or no), coffee consumption (almost never and <1, 1, or ≤2 cups/d), green tea consumption (almost never and <1, 1, 2–3, or ≤4 cups/d), energy intake (continuous), intake of salt (quintile), non-CV (quintile), fruit (quintile), occupation (agriculture/forestry/fishery, salaried/professional, self-employed, housework/unemployed, or other) and screening examination (yes or no).
[c] Analysed after the exclusion of participants who died in the first 5 years of follow-up.

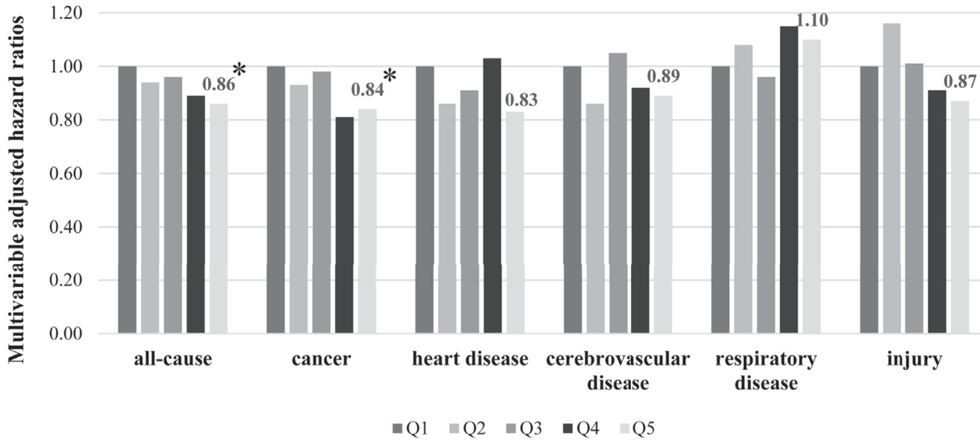

Fig. 1. Association between cruciferous vegetable intake and all-cause, cause-specific mortality in men; Abbreviation: Q, quintile. *Statistical significance level is <0.05.

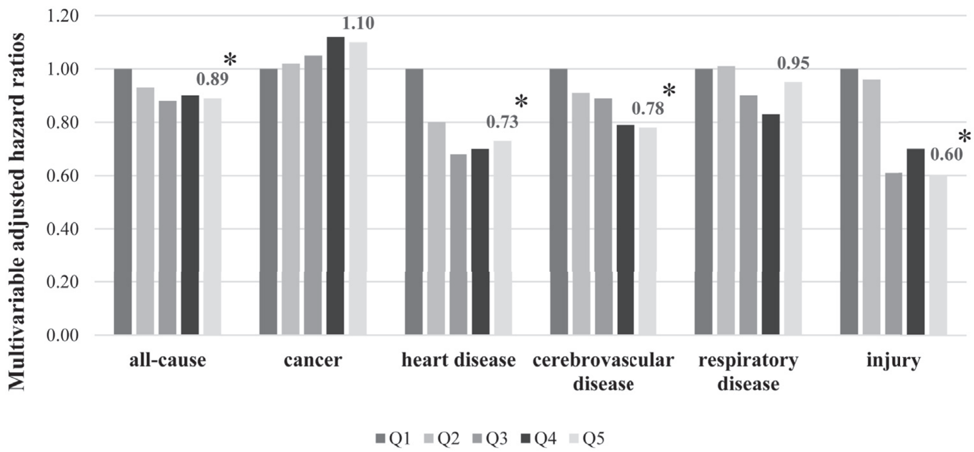

Fig. 2. Association between cruciferous vegetable intake and all-cause, cause-specific mortality in women. Abbreviation: Q, quintile. *Statistical significance level is <0.05.

unchanged when analyses between frequencies of individual cruciferous vegetable intake and risk of mortality were conducted (data not shown).

4. Discussion

According to our knowledge, this is the first study to evaluate the association between cruciferous vegetable intake and five leading mortality causes. Comprehensive analysis revealed an inverse association between cruciferous vegetable intake and all-cause mortality. Compared with the participants in the first quintile of cruciferous vegetable intake, those in the fifth quintile of cruciferous vegetable intake had a lower risk of all-cause mortality (men, 14% and women, 11%). In men, this inverse relationship was predominantly associated with cancer mortality; in women, this relationship was predominantly associated with heart disease, cerebrovascular disease, and injury-related mortality. Moreover, cruciferous vegetable intake was inversely associated with cancer mortality among smokers and heavy drinkers, as well as with heart disease mortality among moderate drinkers in men.

Our findings are consistent with previous findings [15,16] of an inverse association between cruciferous vegetable intake and cardiovascular disease mortality. In the present study, a significant inverse association was found between cruciferous vegetable intake and heart and cerebrovascular diseases in women, but the association was non-significant in men. The effect of cruciferous vegetables in preventing cardiovascular diseases has recently attracted attention [26]. Sulforaphane, an isothiocyanate, reduces oxidative stress and inflammation in the circulatory system by the activation of transcription factor Nrf2 [2,3]. Sulforaphane and other types of isothiocyanates may exhibit anti-inflammatory properties by modulating toll-like receptor 4 signalling, as well as by modifying pro-inflammatory cytokine macrophage migration inhibitors [4]. Numerous studies have reported the potential anticancer properties of cruciferous vegetables. However, because their intake has been shown to reduce the risk of certain types of cancer [27–33], no study has definitively demonstrated either a positive or negative association between cruciferous vegetable intake and cancer mortality. Several factors may explain this observation. First, one of the studies was conducted in the United States, where cruciferous vegetable intake is much less than that in Asian countries [16]. Second, a study conducted in Japan reported that intake of green and yellow vegetables, including cruciferous vegetables, was marginally inversely associated with cancer mortality [34], and the observed decreases in mortality risk were primarily attributed to liver cancer. The present findings of an inverse association between the two factors in men could possibly be explained by the protective properties of isothiocyanates.

In this study, a sex-related discrepancy was observed in the association between cruciferous vegetable intake and cancer mortality risk. Subgroup analysis by smoking status detected a significant inverse association between cruciferous vegetable intake and

Table 4
Multivariable adjusted hazard ratios of all-cause and cause-specific mortality according to cruciferous vegetable intake by smoking status among men.[a]

	Quintile of CV intake					*P*-trend
	Lowest	Second	Third	Fourth	Highest	
All-cause mortality						
Never smokers (n = 13,606)						
No. of cases (n = 2551)	435	437	492	544	643	
Multivariable adjusted HR[b]	1.00 (reference)	0.92 (0.80, 1.05)	0.95 (0.83, 1.09)	0.86 (0.74, 0.99)	0.86 (0.74, 1.00)	0.04
Multivariable adjusted HR[c]	1.00 (reference)	0.89 (0.79, 1.04)	0.95 (0.82, 1.11)	0.86 (0.73, 1.00)	0.86 (0.73, 1.02)	0.09
Ever smokers (n = 27,016)						
No. of cases (n = 7037)	1382	1288	1372	1406	1589	
Multivariable adjusted HR[b]	1.00 (reference)	0.95 (0.88, 1.03)	0.97 (0.90, 1.06)	0.91 (0.84, 1.00)	0.87 (0.80, 1.00)	0.004
Multivariable adjusted HR[c]	1.00 (reference)	0.97 (0.89, 1.06)	0.99 (0.90, 1.08)	0.95 (0.86, 1.04)	0.92 (0.83, 1.02)	0.10
Cancer						
Never smokers						
No. of cases (n = 937)	149	159	202	182	245	
Multivariable adjusted HR[b]	1.00 (reference)	0.90 (0.72, 1.14)	1.04 (0.83, 1.31)	0.77 (0.60, 0.98)	0.91 (0.70, 1.17)	0.25
Multivariable adjusted HR[c]	1.00 (reference)	0.88 (0.68, 1.14)	1.03 (0.80, 1.33)	0.77 (0.58, 1.01)	0.94 (0.71, 1.25)	0.52
Ever smokers						
No. of cases (n = 2944)	568	554	596	565	661	
Multivariable adjusted HR[b]	1.00 (reference)	0.95 (0.84, 1.07)	0.97 (0.85, 1.10)	0.83 (0.73, 0.95)	0.83 (0.72, 0.96)	0.002
Multivariable adjusted HR[c]	1.00 (reference)	0.96 (0.84, 1.10)	0.98 (0.85, 1.13)	0.85 (0.73, 0.99)	0.87 (0.74, 1.02)	0.03
Heart disease						
Never smokers						
No. of cases (n = 351)	57	69	58	85	82	
Multivariable adjusted HR[b]	1.00 (reference)	1.14 (0.79, 1.64)	0.88 (0.60, 1.31)	1.09 (0.74, 1.59)	0.89 (0.58, 1.35)	0.52
Multivariable adjusted HR[c]	1.00 (reference)	1.12 (0.75, 1.67)	0.95 (0.62, 1.45)	1.14 (0.75, 1.72)	0.89 (0.56, 1.40)	0.63
Ever smokers						
No. of cases (n = 841)	172	130	161	194	184	
Multivariable adjusted HR[b]	1.00 (reference)	0.77 (0.61, 0.98)	0.93 (0.74, 1.18)	1.03 (0.81, 1.31)	0.84 (0.64, 1.09)	0.82
Multivariable adjusted HR[c]	1.00 (reference)	0.88 (0.68, 1.14)	0.90 (0.69, 1.18)	1.10 (0.84, 1.43)	0.93 (0.69, 1.25)	0.80
Cerebrovascular disease						
Never smokers						
No. of cases (n = 242)	45	36	46	50	65	
Multivariable adjusted HR[b]	1.00 (reference)	0.73 (0.46, 1.15)	0.88 (0.56, 1.38)	0.74 (0.46, 1.17)	0.80 (0.49, 1.31)	0.49
Multivariable adjusted HR[c]	1.00 (reference)	0.81 (0.49, 1.33)	0.92 (0.55, 1.52)	0.85 (0.51, 1.42)	0.93 (0.54, 1.60)	0.93
Ever smokers						
No. of cases (n = 614)	115	101	131	126	141	
Multivariable adjusted HR[b]	1.00 (reference)	0.91 (0.69, 1.21)	1.14 (0.86, 1.50)	1.00 (0.74, 1.34)	0.93 (0.68, 1.27)	0.83
Multivariable adjusted HR[c]	1.00 (reference)	0.87 (0.64, 1.19)	1.16 (0.86, 1.57)	1.04 (0.76, 1.44)	0.94 (0.67, 1.33)	0.92
Respiratory disease						
Never smokers						
No. of cases (n = 233)	34	42	39	55	63	
Multivariable adjusted HR[b]	1.00 (reference)	1.31 (0.82, 2.10)	1.07 (0.65, 1.77)	1.20 (0.73, 1.96)	1.17 (0.70, 1.98)	0.76
Multivariable adjusted HR[c]	1.00 (reference)	1.16 (0.71, 1.90)	0.87 (0.51, 1.49)	1.04 (0.62, 1.75)	0.98 (0.56, 1.69)	0.80
Ever smokers						
No. of cases (n = 532)	99	92	84	116	141	
Multivariable adjusted HR[b]	1.00 (reference)	1.04 (0.77, 1.39)	0.94 (0.68, 1.28)	1.18 (0.86, 1.61)	1.12 (0.81, 1.57)	0.35
Multivariable adjusted HR[c]	1.00 (reference)	1.09 (0.80, 1.48)	0.94 (0.67, 1.31)	1.22 (0.88, 1.69)	1.18 (0.84, 1.68)	0.26
Injury						
Never smokers						
No. of cases (n = 227)	40	46	45	49	47	
Multivariable adjusted HR[b]	1.00 (reference)	1.13 (0.73, 1.76)	1.05 (0.66, 1.67)	1.04 (0.64, 1.68)	0.87 (0.51, 1.49)	0.54
Multivariable adjusted HR[c]	1.00 (reference)	1.05 (0.63, 1.76)	1.18 (0.70, 1.99)	0.91 (0.52, 1.61)	0.84 (0.45, 1.57)	0.50
Ever smokers						
No. of cases (n = 513)	112	123	101	85	92	
Multivariable adjusted HR[b]	1.00 (reference)	1.17 (0.90, 1.53)	0.98 (0.73, 1.31)	0.84 (0.61, 1.16)	0.86 (0.61, 1.22)	0.12
Multivariable adjusted HR[c]	1.00 (reference)	1.05 (0.77, 1.45)	0.98 (0.69, 1.38)	0.76 (0.52, 1.12)	0.75 (0.50, 1.15)	0.07
Other causes						
Never smokers						
No. of cases (n = 561)	110	85	102	123	141	
Multivariable adjusted HR[b]	1.00 (reference)	0.73 (0.54, 0.98)	0.80 (0.60, 1.07)	0.77 (0.57, 1.03)	0.70 (0.51, 0.96)	0.08
Multivariable adjusted HR[c]	1.00 (reference)	0.72 (0.52, 0.98)	0.81 (0.60, 1.11)	0.77 (0.56, 1.06)	0.69 (0.49, 0.97)	0.10
Ever smokers						
No. of cases (n = 1593)	316	288	299	320	370	
Multivariable adjusted HR[b]	1.00 (reference)	0.96 (0.81, 1.13)	0.96 (0.81, 1.15)	0.94 (0.78, 1.12)	0.88 (0.73, 1.07)	0.22
Multivariable adjusted HR[c]	1.00 (reference)	1.00 (0.84, 1.20)	0.99 (0.82, 1.19)	0.98 (0.81, 1.19)	0.95 (0.78, 1.18)	0.63

Abbreviations: CV, cruciferous vegetables; HR, hazard ratio; CI, confidence interval.

[a] A Cox regression model was used to estimate HRs and 95% CIs.

[b] Adjusted for age (continuous), study area (10 PHC area categories), BMI (<18.5, 18.5–25, 25–30, or >30), smoking status (never; past; current: <10, 10–19, 20–29, 30–39, or ≥40 cigarettes/d), alcohol consumption (non-drinker; current drinker: 1–150, 151–300, 301–450 or ≥451 g ethanol/wk), physical activity (metabolic equivalent, task h/d; continuous), history of hypertension (yes or no), history of diabetes (yes or no), coffee consumption (almost never and <1, 1, or ≤2 cups/d), green tea consumption (almost never and <1, 1, 2–3, or ≤4 cups/d), energy intake (continuous), intake of salt (quintile), non-CV (quintile), fruit (quintile), occupation (agriculture/forestry/fishery, salaried/professional, self-employed, housework/unemployed, or other) and screening examination (yes or no).

[c] Analysed after the exclusion of participants who died in the first 5 years of follow-up.

Table 5
Multivariable adjusted hazard ratios of all-cause and cause-specific mortality according to cruciferous vegetable intake by drinking status among men.[a]

	Quintile of CV intake					*P*-trend
	Lowest	Second	Third	Fourth	Highest	
All-cause mortality						
Non-drinker (n = 10,047)						
No. of cases (n = 2908)	441	461	513	634	859	
Multivariate adjusted HR[b]	1.00 (reference)	1.01 (0.88, 1.15)	1.05 (0.91, 1.20)	1.02 (0.89, 1.18)	1.00 (0.86, 1.15)	0.95
Multivariate adjusted HR[c]	1.00 (reference)	1.02 (0.88, 1.19)	1.03 (0.88, 1.21)	1.05 (0.90, 1.23)	1.04 (0.89, 1.22)	0.58
Moderate drinker, <300 g ethanol/wk (n = 17,569)						
No. of cases (n = 3534)	542	628	709	770	885	
Multivariate adjusted HR[b]	1.00 (reference)	0.93 (0.83, 1.05)	0.92 (0.82, 1.04)	0.88 (0.78, 1.00)	0.84 (0.74, 0.96)	0.01
Multivariate adjusted HR[c]	1.00 (reference)	0.95 (0.83, 1.08)	0.96 (0.85, 1.10)	0.91 (0.79, 1.04)	0.90 (0.77, 1.04)	0.13
Heavy drinker, ≥300 g ethanol/wk (n = 12,571)						
No. of cases (n = 2989)	810	621	613	510	435	
Multivariate adjusted HR[b]	1.00 (reference)	0.93 (0.83, 1.03)	0.95 (0.85, 1.07)	0.81 (0.71, 0.92)	0.77 (0.67, 0.92)	0.0002
Multivariate adjusted HR[c]	1.00 (reference)	0.93 (0.83, 1.05)	0.96 (0.85, 1.09)	0.83 (0.72, 0.96)	0.79 (0.67, 0.93)	0.002
Cancer						
Non-drinker						
No. of cases (n = 1096)	162	167	208	245	314	
Multivariate adjusted HR[b]	1.00 (reference)	0.94 (0.75, 1.16)	1.08 (0.86, 1.35)	0.98 (0.79, 1.23)	0.92 (0.73, 1.17)	0.56
Multivariate adjusted HR[c]	1.00 (reference)	0.97 (0.75, 1.26)	1.12 (0.87, 1.46)	1.04 (0.80, 1.36)	1.04 (0.79, 1.37)	0.69
Moderate drinker, <300 g ethanol/wk						
No. of cases (n = 1472)	208	263	313	303	385	
Multivariate adjusted HR[b]	1.00 (reference)	0.99 (0.82, 1.19)	1.03 (0.85, 1.24)	0.87 (0.72, 1.07)	0.94 (0.76, 1.16)	0.29
Multivariate adjusted HR[c]	1.00 (reference)	1.01 (0.82, 1.25)	1.11 (0.90, 1.37)	0.93 (0.74, 1.16)	1.02 (0.81, 1.29)	0.80
Heavy drinker, ≥300 g ethanol/wk						
No. of cases (n = 1258)	338	278	266	188	188	
Multivariate adjusted HR[b]	1.00 (reference)	0.92 (0.78, 1.08)	0.90 (0.75, 1.07)	0.63 (0.52, 0.78)	0.71 (0.56, 0.89)	<0.0001
Multivariate adjusted HR[c]	1.00 (reference)	0.92 (0.77, 1.10)	0.87 (0.72, 1.06)	0.63 (0.50, 0.79)	0.69 (0.54, 0.88)	<0.0001
Heart disease						
Non-drinker						
No. of cases (n = 386)	61	58	64	94	109	
Multivariate adjusted HR[b]	1.00 (reference)	0.91 (0.63, 1.33)	0.97 (0.67, 1.42)	1.18 (0.81, 1.70)	1.00 (0.68, 1.48)	0.58
Multivariate adjusted HR[c]	1.00 (reference)	0.97 (0.64, 1.47)	0.86 (0.55, 1.33)	1.23 (0.81, 1.86)	0.98 (0.63, 1.52)	0.68
Moderate drinker, <300 g ethanol/wk						
No. of cases (n = 443)	71	80	85	108	99	
Multivariate adjusted HR[b]	1.00 (reference)	0.88 (0.63, 1.22)	0.80 (0.57, 1.17)	0.85 (0.60, 1.19)	0.62 (0.43, 0.91)	0.03
Multivariate adjusted HR[c]	1.00 (reference)	0.91 (0.64, 1.29)	0.74 (0.51, 1.06)	0.80 (0.55, 1.16)	0.64 (0.43, 0.97)	0.04
Heavy drinker, ≥300 g ethanol/wk						
No. of cases (n = 338)	93	57	65	72	51	
Multivariate adjusted HR[b]	1.00 (reference)	0.77 (0.54, 1.08)	0.95 (0.67, 1.34)	1.09 (0.76, 1.57)	0.97 (0.63, 1.48)	0.60
Multivariate adjusted HR[c]	1.00 (reference)	0.88 (0.60, 1.29)	1.13 (0.77, 1.66)	1.33 (0.89, 1.97)	1.19 (0.75, 1.91)	0.14
Cerebrovascular disease						
Non-drinker						
No. of cases (n = 228)	32	30	44	48	74	
Multivariate adjusted HR[b]	1.00 (reference)	0.91 (0.55, 1.53)	1.24 (0.75, 2.05)	0.98 (0.59, 1.64)	0.97 (0.58, 1.63)	0.88
Multivariate adjusted HR[c]	1.00 (reference)	0.83 (0.48,1.46)	1.17 (0.68, 2.01)	0.95 (0.55, 1.65)	0.91 (0.52, 1.60)	0.83
Moderate drinker, <300 g ethanol/wk						
No. of cases (n = 317)	53	46	72	65	81	
Multivariate adjusted HR[b]	1.00 (reference)	0.73 (0.49, 1.10)	1.01 (0.68, 1.48)	0.81 (0.54, 1.22)	0.88 (0.57, 1.35)	0.78
Multivariate adjusted HR[c]	1.00 (reference)	0.74 (0.48, 1.17)	1.03 (0.68, 1.57)	0.84 (0.53, 1.33)	0.94 (0.58, 1.51)	0.98
Heavy drinker, ≥300 g ethanol/wk						
No. of cases (n = 298)	72	61	58	61	46	
Multivariate adjusted HR[b]	1.00 (reference)	1.00 (0.70, 1.43)	0.97 (0.66, 1.42)	1.03 (0.69, 1.54)	0.86 (0.54, 1.37)	0.66
Multivariate adjusted HR[c]	1.00 (reference)	0.99 (0.67, 1.48)	1.03 (0.67, 1.56)	1.19 (0.77, 1.84)	0.93 (0.56, 1.55)	0.86
Respiratory disease						
Non-drinker						
No. of cases (n = 265)	47	42	40	59	77	
Multivariate adjusted HR[b]	1.00 (reference)	0.95 (0.61, 1.47)	0.85 (0.54, 1.35)	1.02 (0.66, 1.59)	0.93 (0.89, 1.48)	0.94
Multivariate adjusted HR[c]	1.00 (reference)	0.88 (0.55,1.40)	0.66 (0.40, 1.11)	0.85 (0.52, 1.37)	0.80 (0.49, 1.32)	0.49
Moderate drinker, <300 g ethanol/wk						
No. of cases (n = 270)	32	50	45	64	79	
Multivariate adjusted HR[b]	1.00 (reference)	1.39 (0.88, 2.21)	1.11 (0.68, 1.80)	1.44 (0.89, 2.34)	1.41 (0.85, 2.35)	0.26
Multivariate adjusted HR[c]	1.00 (reference)	1.48 (0.91, 2.43)	1.24 (0.74, 2.07)	1.63 (0.98, 2.70)	1.49 (0.87, 2.55)	0.21
Heavy drinker, ≥300 g ethanol/wk						
No. of cases (n = 210)	52	41	34	44	39	
Multivariate adjusted HR[b]	1.00 (reference)	1.13 (0.73, 1.73)	0.95 (0.59, 1.53)	1.13 (0.70, 1.81)	1.10 (0.65, 1.88)	0.74
Multivariate adjusted HR[c]	1.00 (reference)	1.14 (0.74, 1.77)	0.90 (0.56, 1.47)	1.09 (0.67, 1.79)	1.12 (0.65, 1.93)	0.80
Injury						
Non-drinker						
No. of cases (n = 192)	38	46	30	32	46	
Multivariate adjusted HR[b]	1.00 (reference)	1.22 (0.78, 1.90)	0.78 (0.47, 1.31)	0.74 (0.43, 1.25)	0.91 (0.53, 1.56)	0.27
Multivariate adjusted HR[c]	1.00 (reference)	1.18 (0.69, 2.03)	0.94 (0.51, 1.71)	0.67 (0.35,1.29)	0.84 (0.43, 1.65)	0.24
Moderate drinker, <300 g ethanol/wk						
No. of cases (n = 276)	49	57	56	60	54	

(continued on next page)

Table 5 (*continued*)

	Quintile of CV intake					*P*-trend
	Lowest	Second	Third	Fourth	Highest	
Multivariate adjusted HR[b]	1.00 (reference)	0.96 (0.64, 1.42)	0.84 (0.56, 1.27)	0.83 (0.54, 1.27)	0.65 (0.40, 1.06)	0.08
Multivariate adjusted HR[c]	1.00 (reference)	0.88 (0.55,1.39)	0.88 (0.55,1.41)	0.75 (0.46, 1.24)	0.58 (0.33, 1.01)	0.05
Heavy drinker, ≥300 g ethanol/wk						
No. of cases (n = 263)	64	65	59	37	37	
Multivariate adjusted HR[b]	1.00 (reference)	1.32 (0.92, 1.90)	1.35 (0.92, 2.00)	0.99 (0.62, 1.56)	1.15 (0.69, 1.91)	0.90
Multivariate adjusted HR[c]	1.00 (reference)	1.21 (0.78, 1.87)	1.36 (0.86, 2.16)	0.93 (0.53, 1.62)	1.11 (0.60, 2.03)	0.94
Other cause						
Non-drinker						
No. of cases (n = 741)	101	118	127	156	239	
Multivariate adjusted HR[b]	1.00 (reference)	1.15 (0.87, 1.52)	1.16 (0.87, 1.53)	1.13 (0.85, 1.50)	1.19 (0.89, 1.59)	0.38
Multivariate adjusted HR[c]	1.00 (reference)	1.21 (0.90, 1.63)	1.18 (0.86, 1.60)	1.22 (0.90, 1.66)	1.29 (0.94, 1.77)	0.17
Moderate drinker, <300 g ethanol/wk						
No. of cases (n = 756)	129	132	138	170	187	
Multivariate adjusted HR[b]	1.00 (reference)	0.83 (0.65, 1.07)	0.77 (0.59, 1.00)	0.83 (0.64, 1.09)	0.75 (0.57, 1.00)	0.11
Multivariate adjusted HR[c]	1.00 (reference)	0.85 (0.65, 1.12)	0.82 (0.62, 1.08)	0.87 (0.65, 1.16)	0.82 (0.61, 1.11)	0.34
Heavy drinker, ≥300 g ethanol/wk						
No. of cases (n = 623)	191	119	131	108	74	
Multivariate adjusted HR[b]	1.00 (reference)	0.81 (0.64, 1.03)	0.94 (0.73, 1.20)	0.78 (0.59, 1.03)	0.58 (0.42, 0.82)	0.007
Multivariate adjusted HR[c]	1.00 (reference)	0.82 (0.63, 1.06)	0.94 (0.72, 1.23)	0.78 (0.58, 1.05)	0.60 (0.42, 0.85)	0.01

Abbreviations: CV, cruciferous vegetables; HR, hazard ratio; CI, confidence interval.

[a] A Cox regression model was used to estimate HRs and 95% CIs.

[b] Adjusted for age (continuous), study area (10 PHC area categories), BMI (<18.5, 18.5–25, 25–30, or >30), smoking status (never; past; current: <10, 10–19, 20–29, 30–39, or ≥40 cigarettes/d), alcohol consumption (non-drinker; current drinker: 1–150, 151–300, 301–450 or ≥451 g ethanol/wk), physical activity (metabolic equivalent, task h/d; continuous), history of hypertension (yes or no), history of diabetes (yes or no), coffee consumption (almost never and <1, 1, or ≤2 cups/d), green tea consumption (almost never and <1, 1, 2–3, or ≤4 cups/d), energy intake (continuous), intake of salt (quintile), non-CV (quintile), fruit (quintile), occupation (agriculture/forestry/fishery, salaried/professional, self-employed, housework/unemployed, or other) and screening examination (yes or no).

[c] Analysed after the exclusion of participants who died in the first 5 years of follow-up.

cancer mortality in men who smoked. This could possibly be because of the reduced bioactivation of procarcinogens in tobacco smoke. In a recent randomized, crossover intervention, 2-phenethyl isothiocyanate (40 mg/d for 5 d) significantly reduced (7.7%) the activation of cigarette-specific lung carcinogens in smokers [35]. However, epidemiological studies on the beneficial effects of cruciferous vegetables against lung cancer within smoking strata have yielded conflicting results. Gao et al. [36] reported that the beneficial effect of cruciferous vegetables was the strongest in current smokers. Conversely, Steinmetz et al. [37] reported this effect only among past smokers. Notably, no study has conducted subgroup analysis by the smoking status to determine the association between cruciferous vegetable intake and cancer mortality [16,17]. Another subgroup analysis by drinking status showed that despite being a heavy drinker, those who are categorized in the highest quintile of cruciferous vegetable intake showed a decreased risk of cancer mortality compared to the lowest quintile. One of the possible explanations is that cruciferous vegetables are also broken down to form another biologically active compound called indoles. Indoles have been shown to have preventive effect against ethanol-induced liver injury by the regulation of ethanol metabolic enzymes, attenuation of oxidative injury, and acceleration of collagen degradation in animal studies [38,39]. Those with high cruciferous vegetable intake may have a greater capacity in the attenuation of oxidative stress and inflammation. However, based on the fact that heavy drinkers tend to smoke more, in our study [40], we additionally conducted an analysis to assess the association between cruciferous vegetable intake and cancer mortality stratified by the combination of smoking and drinking status; the result showed that among non-smokers and heavy drinkers, cruciferous vegetable intake were associated significantly with cancer mortality in men (HR: 0.53; 95% CI: 0.31, 0.91; $P = 0.003$ for trend). Hence, the decreased risk is likely to be due to the beneficial effect of the high cruciferous vegetable intake. We also observed a significant inverse association between cruciferous vegetable intake and heart disease mortality among moderate drinkers. However, the mechanism behind the association between cruciferous vegetable intake and heart disease mortality among moderate drinkers is unknown.

On the other hand, a null association was observed between cruciferous vegetable intake and cancer mortality in women, which remained unchanged when the analysis was restricted to never smokers or non-drinkers. Our findings are in line with previous findings of null associations between cruciferous vegetable intake and cancer mortality in women [17], but the sex-related discrepancy observed in the current study may be explained by the smoking and drinking status.

Our group previously identified a non-significant association between cruciferous vegetable intake and the risk of cardiovascular disease and cancer [41]. Contrastingly, our present study showed an inverse association between cruciferous vegetable intake and cancer mortality among men. This discrepancy may be explained by sex differences because Takachi et al. [41] investigated the association in the entire population, with no sex-specific subgroup analyses. Unexpected gaps between incidence and mortality may be explained by several other factors. Tang et al. [8] concluded that the intake of cruciferous vegetables modifies survival in patients with bladder cancer. Similarly, Wu et al. [7] found that a higher intake of cruciferous vegetable was significantly associated with lung cancer survival in women. Therefore, cruciferous vegetable intake may improve cancer prognosis. Other interpretations based on health-related behaviour may also explain the difference. In the present study, participants in the fifth quintile of cruciferous vegetable intake had a higher percentage of screening experience than did those in the first quintile. In this case, their screening behaviour may have been beneficial for reducing the risk of cancer and cardiovascular disease mortality. Further clarification regarding cancer and cardiovascular disease survival, as well as screening behaviour is necessary.

Aside the cardiovascular disease and cancer mortality, cruciferous vegetable intake also showed a significant association with injury-related mortality in women. We have identified the two most frequent causes of injury-related mortality as accidents (58%

Table 6
Multivariable hazard ratios of all-cause according to specific cruciferous vegetable intake.[a]

	Men (n = 40,622)				Women (n = 47,562)			
	Tertile of CV intake				Tertile of CV intake			
	None/Low	Medium	High	*P* for trend	None/Low	Medium	High	*P* for trend
Cabbage								
No. of cases	3431	3067	3090	–	2178	1748	1835	
Median intake (g/d)	3	11	24	–	4	13	26	
Age- and area-adjusted HR	1.00 (reference)	0.92 (0.88, 0.97)	0.88 (0.84, 0.93)	<0.0001	1.00 (reference)	0.90 (0.84, 0.96)	0.90 (0.85, 0.96)	0.001
Multivariable adjusted HR[b]	1.00 (reference)	1.00 (0.95, 1.06)	0.97 (0.92, 1.03)	0.38	1.00 (reference)	0.95 (0.89, 1.02)	0.97 (0.90, 1.04)	0.34
Multivariable adjusted HR[c]	1.00 (reference)	1.01 (0.95, 1.07)	0.99 (0.93, 1.06)	0.77	1.00 (reference)	0.95 (0.88, 1.02)	0.97 (0.89, 1.05)	0.37
Chinese radish								
No. of cases	3030	3023	3535	–	1886	1812	2063	
Median intake (g/d)	6	17	38	–	7	21	43	
Age- and area-adjusted HR	1.00 (reference)	0.88 (0.84, 0.93)	0.87 (0.82, 0.91)	<0.0001	1.00 (reference)	0.91 (0.86, 0.97)	0.87 (0.82, 0.93)	<0.0001
Multivariable adjusted HR[b]	1.00 (reference)	0.95 (0.89, 1.00)	0.94 (0.88, 1.00)	0.04	1.00 (reference)	0.99 (0.92, 1.06)	0.92 (0.85, 0.99)	0.02
Multivariable adjusted HR[c]	1.00 (reference)	0.93 (0.87, 0.99)	0.94 (0.88, 1.00)	0.07	1.00 (reference)	1.02 (0.94, 1.10)	0.93 (0.86, 1.01)	0.09
Komatsuna								
No. of cases	4429	2443	2716		2366	1643	1752	
Median intake (g/d)	0	1	3		0	1	4	
Age- and area-adjusted HR	1.00 (reference)	0.99 (0.94, 1.04)	0.92 (0.88, 0.97)	0.002	1.00 (reference)	0.88 (0.82, 0.94)	0.86 (0.80, 0.92)	<0.0001
Multivariable adjusted HR[b]	1.00 (reference)	1.05 (1.00, 1.11)	1.02 (0.96, 1.08)	0.41	1.00 (reference)	0.95 (0.88, 1.02)	0.98 (0.91, 1.05)	0.52
Multivariable adjusted HR[c]	1.00 (reference)	1.06 (1.00, 1.13)	1.04 (0.97, 1.10)	0.25	1.00 (reference)	0.95 (0.88, 1.03)	0.98 (0.91, 1.07)	0.65
Broccoli								
No. of cases	3615	2953	3020		2222	1844	1695	
Median intake (g/d)	0	2	6		1	3	9	
Age- and area-adjusted HR	1.00 (reference)	0.87 (0.82, 0.91)	0.81 (0.78, 0.86)	<0.0001	1.00 (reference)	0.90 (0.85, 0.96)	0.83 (0.78, 0.89)	<0.0001
Multivariable adjusted HR[b]	1.00 (reference)	0.92 (0.87, 0.96)	0.91 (0.86, 0.96)	0.0005	1.00 (reference)	0.93 (0.87, 0.99)	0.88 (0.82, 0.94)	0.0003
Multivariable adjusted HR[c]	1.00 (reference)	0.92 (0.87, 0.97)	0.90 (0.85, 0.96)	0.0006	1.00 (reference)	0.92 (0.86, 0.99)	0.88 (0.81, 0.95)	0.0007
Chinese leaves								
No. of cases	3144	3006	3438		1939	1759	2063	
Median intake (g/d)	1	4	12		1	5	13	
Age- and area-adjusted HR	1.00 (reference)	0.92 (0.88, 0.97)	0.90 (0.85, 0.94)	<0.0001	1.00 (reference)	0.92 (0.86, 0.98)	0.95 (0.89, 1.01)	0.12
Multivariable adjusted HR[b]	1.00 (reference)	0.99 (0.94, 1.04)	0.99 (0.93, 1.05)	0.68	1.00 (reference)	0.99 (0.93, 1.06)	1.07 (0.99, 1.15)	0.07
Multivariable adjusted HR[c]	1.00 (reference)	0.99 (0.93, 1.05)	1.00 (0.94, 1.07)	0.95	1.00 (reference)	1.00 (0.93, 1.07)	1.07 (0.99, 1.16)	0.09
Pak choi								
No. of cases	5438	2002	2148		2815	1423	1523	
Median intake (g/d)	0	2	8		0	2	9	
Age- and area-adjusted HR	1.00 (reference)	0.95 (0.90, 1.00)	0.90 (0.86, 0.95)	<0.0001	1.00 (reference)	0.86 (0.81, 0.92)	0.84 (0.79, 0.90)	<0.0001
Multivariable adjusted HR[b]	1.00 (reference)	1.03 (0.97, 1.09)	0.99 (0.93, 1.05)	0.91	1.00 (reference)	0.93 (0.87, 1.00)	0.93 (0.86, 1.00)	0.03
Multivariable adjusted HR[c]	1.00 (reference)	1.01 (0.95, 1.08)	0.99 (0.92, 1.05)	0.72	1.00 (reference)	0.94 (0.87, 1.02)	0.95 (0.87, 1.02)	0.15
Leaf mustard								
No. of cases	6644	1416	1528		3962	860	939	
Median intake (g/d)	0	2	7		0	2	8	
Age- and area-adjusted HR	1.00 (reference)	0.96 (0.90, 1.02)	0.94 (0.88, 1.00)	0.04	1.00 (reference)	0.94 (0.87, 1.01)	0.94 (0.87, 1.02)	0.09
Multivariable adjusted HR[b]	1.00 (reference)	1.00 (0.94, 1.07)	1.00 (0.93, 1.07)	0.99	1.00 (reference)	1.05 (0.97, 1.14)	1.06 (0.97, 1.15)	0.23
Multivariable adjusted HR[c]	1.00 (reference)	1.02 (0.95, 1.10)	1.00 (0.92, 1.08)	0.98	1.00 (reference)	1.04 (0.95, 1.13)	1.04 (0.94, 1.14)	0.41
Pickled Chinese radish								
No. of cases	2372	3373	3843		1312	2023	2426	
Median intake (g/d)	0	2	12		0	2	15	
Age- and area-adjusted HR	1.00 (reference)	0.89 (0.84, 0.93)	0.85 (0.80, 0.89)	<0.0001	1.00 (reference)	0.90 (0.84, 0.97)	0.85 (0.79, 0.91)	<0.0001
Multivariable adjusted HR[b]	1.00 (reference)	0.95 (0.90, 1.00)	0.90 (0.85, 0.95)	0.0003	1.00 (reference)	0.97 (0.90, 1.04)	0.94 (0.87, 1.02)	0.12
Multivariable adjusted HR[c]	1.00 (reference)	0.98 (0.92, 1.04)	0.94 (0.89, 1.01)	0.08	1.00 (reference)	0.96 (0.89, 1.04)	0.95 (0.88, 1.04)	0.28
Pickled rape and leaf mustard								
No. of cases	3122	3006	3460		1916	1765	2080	
Median intake (g/d)	0	1	10		0	1	11	
Age- and area-adjusted HR	1.00 (reference)	0.91 (0.87, 0.96)	0.93 (0.88, 0.98)	0.009	1.00 (reference)	0.92 (0.86, 0.99)	0.92 (0.86, 0.99)	0.02
Multivariable adjusted HR[b]	1.00 (reference)	0.97 (0.92, 1.03)	0.98 (0.92, 1.05)	0.65	1.00 (reference)	1.02 (0.94, 1.09)	1.04 (0.96, 1.12)	0.37
Multivariable adjusted HR[c]	1.00 (reference)	0.98 (0.92, 1.05)	0.98 (0.91, 1.05)	0.57	1.00 (reference)	0.98 (0.91, 1.07)	1.00 (0.92, 1.08)	0.94
Pickled Chinese leaves								
No. of cases	3144	2956	3488		1912	1776	2073	
Median intake (g/d)	1	3	11		0	3	12	
Age- and area-adjusted HR	1.00 (reference)	0.97 (0.92, 1.03)	0.95 (0.90, 1.01)	0.08	1.00 (reference)	0.94 (0.87, 1.00)	0.89 (0.83, 0.95)	0.94
Multivariable adjusted HR[b]	1.00 (reference)	1.02 (0.97, 1.08)	1.02 (0.96, 1.08)	0.61	1.00 (reference)	0.96 (0.89, 1.03)	0.94 (0.87, 1.02)	0.14
Multivariable adjusted HR[c]	1.00 (reference)	1.02 (0.96, 1.09)	1.03 (0.96, 1.11)	0.38	1.00 (reference)	1.00 (0.96, 1.04)	0.96 (0.88, 1.04)	0.26

Abbreviations: CV, cruciferous vegetables; SD, standard deviation.
[a] A Cox regression model was used to estimate HRs and 95% CIs.
[b] Adjusted for age, study area, BMI, smoking status, alcohol consumption, physical activity, history of hypertension, history of diabetes, coffee consumption, green tea consumption, energy intake, intake of salt, non-CV, fruit, occupation, screening examination, and mutually adjusted for all the variables in the table.
[c] Analysed after the exclusion of participants who died in the first 5 years of follow-up.

in both gender) and suicides (40% in both gender). Several studies have reported that cruciferous vegetable intake is associated with less cognitive decline [18,19]. A cross-sectional survey revealed that cognitive function was significantly associated with food-related choking [42]; while executive function, working memory, attention, and speed of information processing, are all essential cognitive factors for safe driving [43]. With suicides, our study group previously reported that prudent dietary pattern characterized by a high intake of vegetables, fruits, potatoes, soy products, mushrooms, seaweed, and fish was associated with a decreased risk of suicide [44]. A possible reason for the observed inverse association between injury-related deaths among female is due to folates and other antioxidant vitamins found abundantly in cruciferous vegetables, as they are known to prevent depressive symptoms. Thus, improvement of cognitive function and prevention of depression may play an important role in the reduction of injury-related mortality risk.

Our study also found a significant inverse association between broccoli and Chinese radish intake and all-cause mortality, regardless of gender. Similarly, a previous study reported that broccoli consumption was inversely associated with total mortality among patients with bladder cancer [8]. Furthermore, a case-controlled study reported an inverse association between broccoli intake and colorectal cancer risk [45].

This study had numerous strengths, including its prospective design, recruitment of a general Japanese population with a high response rate, and a small proportion of loss to follow-up. However, the study also had several limitations. First, cruciferous vegetable intake derived from the FFQ could have been misclassified. Nonetheless, even if the misclassification of cruciferous vegetable intake occurred, the bias may have been non-differential and therefore may have caused an underestimation of the risk of mortality. Regardless, a significant inverse association was found between total cruciferous vegetable intake and mortality risk. Second, there may be the potential influence of subclinical illnesses in participants that might have modified their diet. Therefore, we conducted a 5-year lagged analysis by excluding deaths reported within the 5 years of follow-up. However, the results essentially remained unchanged. Third, information on the cooking methods for cruciferous vegetable was unavailable; since studies have reported that raw cruciferous vegetables have a higher bioavailability of isothiocyanate [46,47]. Fourth, cruciferous vegetable intake may represent a healthy eating behaviour which might have confounded the association between cruciferous vegetable intake and mortality. Therefore, the intake of fruit and other vegetables was included in the multivariable model for adjustment. Finally, participants who consumed more cruciferous vegetables were significantly older ($P < 0.0001$). Despite that we included age in our multivariable model, residual effect of age might have remained. To consider the effect of age on the association between cruciferous vegetable intake and mortality as well as cause-specific mortality risks, we conducted subgroup analysis stratified by age categories (results not shown); however, the results remained almost unchanged in both gender.

Further evaluation is warranted to determine whether the differential associations between other individual cruciferous species and total and cause-specific mortality are associated with certain types of isothiocyanates. Epidemiological studies using potential biomarkers, such as urinary isothiocyanate, to assess their direct effect on mortality may be necessary to elucidate the underlying mechanisms.

In conclusion, the present study showed an inverse association of cruciferous vegetable intake with all-cause mortality in men and women (with cancer mortality in men; and heart disease, cerebrovascular disease, and injury-related mortality in women).

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Conflict of interest

All authors declare no conflicts of interest.

Author contributions

NM performed statistical analysis, data interpretation, and manuscript drafting. TS was responsible for critically supervising the study for important intellectual content. HC, MM, M Inoue, AG, RT, JI, MN, and HI reviewed and edited the manuscript and contributed to the discussion; NS, M Iwasaki, and TY contributed to the management of the study, reviewed and edited the manuscript, and contributed to the discussion. ST (principal investigator) obtained the funding, designed, initiated, and organised the study; reviewed and edited the manuscript; and contributed to the discussion.

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All contributing JPHC members (as of March 2018) are shown below: http://epi.ncc.go.jp/en/jphc/781/7951.html.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.clnu.2018.04.012.

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