

Frequency of Seaweed Intake and Its Association with Cardiovascular Disease Mortality: The JACC Study

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Aim: Seaweed is a popular traditional foodstuff in Asian countries. To our knowledge, few studies have examined the association of seaweed intake with mortality from cardiovascular disease. We examined the association of frequency of seaweed intake with total and specific cardiovascular disease mortality.

Methods: We examined the association of seaweed intake with mortality from cardiovascular disease among 40,234 men and 55,981 women who participated in the Japan Collaborative Cohort Study for Evaluation of Cancer Risk. Sex-specific hazard ratios for mortality from cardiovascular disease (stroke, stroke subtypes, and coronary heart disease) according to the frequency of seaweed intake were calculated stratified by study area and adjusted for potential cardiovascular risk factors and dietary factors.

Results: During the 1,580,996 person-year follow-up, 6,525 cardiovascular deaths occurred, of which 2,820 were due to stroke, and 1,378, to coronary heart disease. Among men, the multivariable analysis showed that participants who ate seaweed almost every day compared with those who never ate seaweed had hazard ratios (95% confidence interval; *P* for trend) of 0.79 (0.62–1.01; 0.72) for total cardiovascular disease, 0.70 (0.49–0.99; 0.47) for total stroke, 0.69 (0.41–1.16; 0.11) for cerebral infarction. Among women, the multivariable-adjusted hazard ratios were 0.72 (0.55–0.95; 0.001) for total cardiovascular disease, 0.70 (0.46–1.06; 0.01) for total stroke, and 0.49 (0.27–0.90; 0.22) for cerebral infarction. No associations were observed between seaweed intake and risk of intraparenchymal hemorrhage and coronary heart disease among either men or women.

Conclusions: We found an inverse association between seaweed intake and cardiovascular mortality among Japanese men and women, especially that from cerebral infarction.

Key words: Seaweed, Cohort study, Total cardiovascular disease

Introduction

Seaweed has gained increasing interest for its potential role in cardiovascular disease (CVD) prevention^{1,2}. Seaweed contains dietary fibers, peptides, and carotenoids that have beneficial effects on cardiovascular risk factors including blood pressure³⁻⁷, serum lipids⁸⁻¹⁰, and fatty acid¹¹, blood glucose¹², and body weight^{9, 13, 14}. However, the health effect due to the

combination of these nutrients and other nutrients as food is largely known.

Seaweed is a popular traditional foodstuff in Asian countries, including Japan, Korea, and parts of China. For example, on average, Japanese population consumes 9.9 g of seaweed a day¹⁵. Japan's longest life expectancy and the lowest CVD mortality in the world¹⁶ could be due to their unique dietary patterns¹⁷, which are partly characterized by regular

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intake of seaweed^{18, 19}).

However, few studies have examined the association of seaweed intake with mortality or morbidity from CVD²⁰. It is worth analyzing that association as an important topic in nutritional epidemiology.

Therefore, we investigated here the association of frequency of seaweed intake with total and specific CVD mortality, including total stroke, stroke subtypes (intraparenchymal and subarachnoid hemorrhages and cerebral infarction), and coronary heart disease (CHD) in Japanese.

Methods

Study Cohort

The Japan Collaborative Cohort Study for Evaluation of Cancer Risk (JACC study) was a cohort study sponsored by the Japanese Ministry of Education, Culture, Sports, Science and Technology that comprised a nationwide community-based sample of 110,585 persons (46,395 men and 64,190 women) aged 40 to 79 years during the baseline period (1988–1990) from 45 communities in Japan, as described elsewhere in detail²¹. The study participants completed self-administered questionnaires about their lifestyles, including food intake, and medical histories of CVD or cancer. The participants, methods, measurements, and statistical analyses of the present study were basically the same as those reported in a previous JACC publication²¹. Briefly, we excluded persons who reported a history of heart disease, stroke, or cancer at baseline ($n=6,234$) and those with incomplete answers for seaweed intake in the dietary questionnaire ($n=8,136$). Finally, a total of 96,215 individuals (40,234 men and 55,981 women) participated in the analyses.

Seaweed Intake

The frequency of seaweed intake during the previous year was assessed by food frequency questionnaire (FFQ) from “never,” “1 to 2 times a month,” “1 to 2 times a week,” “3 to 4 times a week,” and “almost every day.” The actual amount of seaweed is difficult to estimate since it is consumed usually as a hot water extract in soup, a flavoring for other foods (dashi), a condiment, or a side dish. However, good reproducibility and validity of the questionnaire were reported (Spearman correlation coefficients of reproducibility=0.66 and validity=0.46)²². In nutritional epidemiology, this level of correlation coefficient is considered acceptable for the evaluation of food intake²³. The FFQ included 33 food items and five choices for frequency of intake offered for each item²². The amounts of nutrients consumed were calculated by multiplying

the frequency scores and estimated nutrients for each portion and summing across all 33 items. The details of the validation study and methods for the estimation of nutrient factors were reported previously²². This FFQ showed moderate validity in many nutrient items.

Mortality Surveillance

The cause and date of death were systematically obtained from death certificates. In Japan, registration of death is required by the Family Registration Law and is followed nationwide. Thus, all deaths that occurred in the cohort were confirmed by death certificates from a public health center, except for persons who died after they had moved from their original community, in which case, the participant was censored. The date of move-out of cohort members from the study area was verified by the investigator in cooperation with key members of the local governmental office. We continued follow-up from the time of the baseline survey through the end of 2009, with the exceptions of four communities through 1999, four communities through 2003, and two communities through 2008. We used the underlying cause of death coded by the 10th Revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) to identify mortality endpoints: total stroke (I60–I69), including intraparenchymal hemorrhage (I61), subarachnoid hemorrhage (I60), and cerebral infarction (I63), CHD (I20–I25), and total CVD (I01–I99).

Statistical Analysis

We calculated age-adjusted means and proportions of selected cardiovascular risk factors and nutrients according to the frequency of seaweed intake, and the overall difference was tested by analysis of covariance. For each participant, we calculated the person-years of follow-up from baseline in 1988–1990 to the first endpoint (death, moving from the community, or the end of 2009). We tested the proportional hazards assumption in Cox regression using risk factors by time interactions and found it was not violated. The sex-specific hazard ratio (HR) with 95% confidence intervals (CIs) of each mortality outcome was calculated according to the frequency of seaweed intake by using the Cox proportional hazards models, stratifying jointly by areas (Hokkaido, Tohoku, Kanto, Chubu, Kinki, Chugoku, and Kyushu) and adjusting for age (continuous). In the multivariable model, we further adjusted for potential confounders, including body mass index (quintiles), history of hypertension and diabetes mellitus (yes or no), alcohol intake (never, former, current drinker of ethanol at 1–22, 23–45,

46–68, or 69 g/day; 23 g ethanol corresponds to 1 *go*, a Japanese traditional unit for volume), smoking status (never, former, current smoker of 1–19, or 20 cigarettes/day), perceived mental stress (low, median, high, or extremely), daily walking time (rarely, 30, 30–60, or more than 60 min/day), sport participation (never, 1–2, 3–4, or >5 h/week), education levels (age of completed education of <13, 13–15, 16–18, or ≥ 19 years), and quartiles of total energy, vegetables, fruit, meat, fish, and salt intakes. Body mass index was calculated as body weight (kg) divided by the square of height (m²) and lifestyles, including weight, height, and histories of hypertension and diabetes, were derived from the self-reported baseline questionnaire. We used SAS version 9.4 software (SAS Institute, Cary, NC) for the analyses. All the probability values for the statistical tests were two-tailed, and values less than 0.05 were regarded as significant.

Ethical Considerations

Informed consent was obtained before the participants completed the questionnaire or sometimes from community leaders instead of individuals, which was a common practice for informed consent in Japan at that time. The JACC study protocol was approved by the institutional review boards of Hokkaido University (i 14-044), the University of Tsukuba (66-3), and Osaka University (14285).

Results

During the 1,580,996 person-year follow-ups, 6,525 deaths from CVD occurred (3,315 men and 3,210 women); of those, 2,820 were from stroke (1,423 men and 1,397 women), and 1,378 were from CHD (776 men and 602 women).

As shown in **Table 1**, seaweed intake was positively associated with age, history of diabetes, sports participation >5 h/week, walking time >1 h/day, and major nutrient intakes, whereas it was inversely associated with current smoking for both men and women. Seaweed intake was positively associated with current drinking for men but inversely for women. High perceived mental stress was inversely associated with seaweed intake only among men. No association was found between the history of hypertension and hours of sleep among either sex.

Table 2 shows the age-adjusted and area-stratified jointly and multivariable-adjusted HRs and 95% CIs for mortality from stroke, stroke subtypes, CHD, and CVD according to the frequency of seaweed intake. Compared with participants who never ate seaweed, both men and women who ate almost every day had lower risk of mortality from total stroke, espe-

cially cerebral infarction, and total CVD, although not always statically significant. Among men, the multivariable-adjusted HRs (95% CIs; *P* for trend) for those who never ate seaweed versus who ate seaweed almost every day were 0.70 (0.49–0.99; 0.47) for total stroke, 0.69 (0.41–1.16; 0.11) for cerebral infarction and 0.79 (0.62–1.01; 0.72) for total CVD. The respective HRs among women were 0.70 (0.46–1.06; 0.01), 0.49 (0.27–0.90; 0.22) and 0.72 (0.55–0.95; 0.001). No associations were observed between seaweed intake and risks of intraparenchymal hemorrhage and CHD among either men or women.

Discussion

We observed that persons who never ate seaweed intake had the higher mortality from total stroke, cerebral infarction, and total CVD, but not from CHD, in this prospective cohort study of Japanese men and women. Our results strengthened the preliminary finding from the JACC study²⁴, which did not perform adjustments for potential confounding variables or stroke subtype classification.

A recent report from the Japan Public Health Center-Based Prospective (JPHC) study of middle-aged Japanese study showed that seaweed intake was inversely associated with the risk of incident ischemic heart disease but not stroke²⁰. As for stroke, different results could be due to different categories of frequencies of seaweed intake. The discrepancy for the result of stroke between JPHC study and the present JACC study may be due to different lowest categories of seaweed intake (never versus <1 day/week). JPHC study did not differentiate the categories of never and <1 day/week in the questionnaire so that the excess risk of stroke in the lowest category of seaweed intake might not be detected, whereas the JACC study found the excess risk of stroke mortality. The discrepancy for the result of CHD may be due to the outcome (incidence versus mortality). As for CHD, validation studies have shown that approximately one-quarter of deaths from CHD as recorded on death certificates were misdiagnosed^{25, 26}. Therefore, the association between seaweed intake and mortality from CHD might be weakened.

These epidemiological findings supported the result from animal experimental studies. Stroke-prone spontaneously hypertensive rats (SHRSPs) fed 10% active fiber (powdered brown seaweed converted to potassium ions form) had the attenuation of development of severe hypertension and stroke compared with SHRSPs fed kaolin⁴. The SHRSPs fed 5% wakame seaweed showed delayed developments of stroke and improved survival compared with the con-

Table 1. Sex-specific age-adjusted baseline characteristics according to the frequency of seaweed intake

	Seaweed intake					P for trend
	Never	< 1-2 times/ month	< 1-2 times / week	3-4 times / week	Almost every day	
Men (n = 40,234)						
Number of subjects	756	4,424	12,444	12,010	10,600	
Age, years	56.7	55.7	56.2	56.9	58.6	< .001
Body mass index, kg/m ²	22.5	22.6	22.6	22.6	22.7	0.01
History of hypertension, %	18.1	19.1	20.2	20.2	20.3	0.15
History of diabetes, %	7.7	5.8	6.3	6.8	7.4	< .001
Current drinker, %	67.3	74.5	75.8	76.9	76.4	< .001
Current smoker, %	58.1	58.1	54.8	52.7	51.2	< .001
High perceived mental stress, %	27.9	23.7	22.9	23.2	22.8	< .001
Hours of sleep, hour/day	7.5	7.4	7.5	7.4	7.5	0.15
Sport participation > 5 hour /week, %	4.3	6.5	7.1	7.7	7.7	0.04
Walking time > 1 hour/day, %	49.5	46.6	48.9	49.8	52.6	< .001
Educated over 18 years old, %	9.6	14.7	13.6	12.0	14.1	0.57
Total energy intake, kcal/day	1,521	1,574	1,705	1,818	1,901	< .001
Vegetables intake, g/day	57.4	57.6	78.8	100.2	123.2	< .001
Fruit intake, g/day	73.0	83.3	107.9	125.6	151.2	< .001
Meats intake, g/day	21.7	22.6	27.6	31.2	33.7	< .001
Fish intake, g/day	37.1	36.2	44.0	51.6	58.5	< .001
Total fiber intake, g/day	9.5	9.7	11.5	13.1	14.8	< .001
Sodium intake, mg/day	1,525	1,632	1,955	2,232	2,447	< .001
Women (n = 55,981)						
Number of subjects	700	3,601	14,297	17,503	19,880	
Age, years	57.9	57.8	57.0	56.7	58.1	< .001
Body mass index, kg/m ²	23.1	23.0	23.0	22.9	22.9	0.01
History of hypertension, %	20.7	22.9	22.3	22.0	22.4	0.35
History of diabetes, %	3.1	4.8	3.4	3.8	4.3	0.003
Current drinker, %	29.3	24.5	25.4	24.5	24.2	0.01
Current smoker, %	10.4	7.5	6.0	5.2	4.1	< .001
High perceived mental stress, %	24.9	20.2	20.1	19.8	20.4	0.57
Hours of sleep, hour/day	7.1	7.1	7.1	7.1	71.1	0.98
Sport participation > 5 hour/week, %	3.6	3.9	4.2	4.7	5.0	0.001
Walking time > 1 hour/day, %	44.8	48.5	51.3	50.8	53.1	0.002
Educated over 18 years old, %	6.4	6.6	6.9	6.8	9.2	< .001
Total energy intake, kcal/day	1,233	1,259	1,357	1,426	1,525	< .001
Vegetables intake, g/day	67.9	68.7	87.2	106.2	131.0	< .001
Fruit intake, g/day	98.6	109.9	128.2	145.2	171.4	< .001
Meats intake, g/day	23.3	22.4	27.3	30.5	33.6	< .001
Fish intake, g/day	34.9	36.5	43.0	49.6	57.4	< .001
Total fiber intake, g/day	9.2	9.4	10.9	12.2	14.0	< .001
Sodium intake, mg/day	1,387	1,485	1,759	1,960	2,213	< .001

trol SHRSPs a normal diet⁵).

The underlying mechanisms responsible for the association between seaweed and CVD have still to be clarified. One possible mechanism is an effect of seaweed on the attenuation of blood pressure inverse observed in one animal study⁴) but not in the other⁵).

Among the seaweeds, wakame is the most widely consumed in Asian society²⁷). Dry wakame (100 g) contains 33 g of dietary fiber, of which the main constituents are alginates. *In vitro* studies showed that alginates acted as an ion exchanger in liquids, absorbing sodium ions from and releasing potassium ions into

Table 2. Multivariable HRs and 95% CIs of mortality from stroke, stroke types, coronary heart disease and total cardiovascular disease according to the frequency of seaweed intake

	Seaweed intake					P for trend
	Never	< 1-2 times / month	< 1-2 times / week	3-4 times / week	Almost every day	
Men						
Person-years	11737	69423	201002	194767	168387	
Total stroke						
Number of case	36	112	398	443	434	
Model 1	1.00	0.54 (0.37-0.79)	0.62 (0.44-0.87)	0.67 (0.47-0.94)	0.63 (0.45-0.89)	0.78
Model 2	1.00	0.56 (0.38-0.82)	0.66 (0.47-0.94)	0.73 (0.51-1.03)	0.70 (0.49-0.99)	0.47
Intraparenchymal hemorrhage						
Number of case	9	34	107	99	84	
Model 1	1.00	0.62 (0.30-1.30)	0.66 (0.33-1.30)	0.60 (0.30-1.20)	0.51 (0.25-1.01)	0.05
Model 2	1.00	0.62 (0.29-1.29)	0.71 (0.36-1.41)	0.68 (0.34-1.36)	0.58 (0.29-1.18)	0.23
Subarachnoid hemorrhage						
Number of case	1	16	32	37	30	
Model 1	1.00	-	-	-	-	-
Model 2	1.00	-	-	-	-	-
Cerebral infarction						
Number of case	16	41	139	176	188	
Model 1	1.00	0.48 (0.27-0.85)	0.51 (0.30-0.86)	0.62 (0.37-1.03)	0.62 (0.37-1.05)	0.12
Model 2	1.00	0.51 (0.28-0.91)	0.55 (0.33-0.94)	0.67 (0.40-1.14)	0.69 (0.41-1.16)	0.11
Coronary heart diseases						
Number of case	12	85	227	237	214	
Model 1	1.00	1.27 (0.69-2.33)	1.13 (0.63-2.02)	1.16 (0.65-2.07)	1.05 (0.58-1.88)	0.23
Model 2	1.00	1.27 (0.69-2.34)	1.17 (0.65-2.11)	1.25 (0.70-2.25)	1.18 (0.66-2.14)	0.92
Total cardiovascular diseases						
Number of case	76	302	951	1011	975	
Model 1	1.00	0.72 (0.56-0.92)	0.73 (0.58-0.92)	0.74 (0.59-0.94)	0.71 (0.56-0.89)	0.22
Model 2	1.00	0.73 (0.57-0.94)	0.77 (0.61-0.98)	0.82 (0.64-1.04)	0.79 (0.62-1.01)	0.72
Women						
Person-years	11552	57276	236264	296428	334161	
Total stroke						
Number of case	25	108	372	411	481	
Model 1	1.00	0.87 (0.56-1.34)	0.76 (0.51-1.15)	0.68 (0.46-1.02)	0.62 (0.46-0.93)	< .0001
Model 2	1.00	0.87 (0.56-1.35)	0.81 (0.54-1.22)	0.74 (0.49-1.12)	0.70 (0.46-1.06)	0.01
Intraparenchymal hemorrhage						
Number of case	4	28	80	78	98	
Model 1	1.00	1.36 (0.48-3.89)	1.00 (0.37-2.73)	0.79 (0.29-2.16)	0.77 (0.28-2.11)	0.02
Model 2	1.00	1.46 (0.51-4.20)	1.16 (0.42-3.20)	1.00 (0.36-2.77)	0.99 (0.36-2.76)	0.20
Subarachnoid hemorrhage						
Number of case	1	22	64	85	84	
Model 1	1.00	-	-	-	-	-
Model 2	1.00	-	-	-	-	-
Cerebral infarction						
Number of case	12	30	123	129	159	
Model 1	1.00	0.51 (0.26-0.99)	0.53 (0.29-0.96)	0.45 (0.25-0.81)	0.42 (0.23-0.76)	0.02
Model 2	1.00	0.49 (0.25-0.97)	0.58 (0.32-1.05)	0.49 (0.27-0.90)	0.49 (0.27-0.90)	0.22
Coronary heart diseases						
Number of case	7	46	146	190	213	
Model 1	1.00	1.43 (0.64-3.16)	1.18 (0.55-2.52)	1.25 (0.59-2.67)	1.14 (0.54-2.43)	0.41
Model 2	1.00	1.33 (0.60-2.96)	1.31 (0.61-2.81)	1.48 (0.69-3.17)	1.42 (0.66-3.05)	0.50
Total cardiovascular diseases						
Number of case	57	240	845	965	1103	
Model 1	1.00	0.87 (0.65-1.16)	0.78 (0.59-1.02)	0.72 (0.55-0.93)	0.64 (0.49-0.83)	< .0001
Model 2	1.00	0.85 (0.64-1.14)	0.83 (0.63-1.09)	0.78 (0.60-1.03)	0.72 (0.55-0.95)	0.001

Abbreviations HR, hazard ratio; CI, confidence intervals

Model 1 was stratified jointly by area and adjusted for age.

Model 2 was adjusted further for body mass index, history of hypertension, history of diabetes, alcohol intake, smoking status, perceived mental stress, walking time, sport participation, education levels, total energy, dietary intake of vegetables, fruits, meat, fish, and salt intake.

liquid media^{28, 29}), and an animal study using SHRSPs showed that alginates inhibited intestinal sodium absorption⁴). Another possible reason for the blood pressure-lowering effect of wakame might be the isolation of peptides from brown seaweed, which had an inhibitory activity for angiotensin 1-converting enzyme, causing an antihypertensive effect in rats⁶). In humans, a randomized double-blind controlled trial demonstrated that among 36 hypertensive Japanese patients (mean age, 71 years), supplementation of 5 g/day of dried wakame powder significantly lowered the diastolic blood pressure by 9 mmHg ($p < 0.01$) at 4 weeks and by 8 mmHg ($p < 0.05$) at 8 weeks when compared with the no-treatment control group⁷). Also, another double-blind controlled trial of 62 untreated mild hypertensive patients (mean age, 48 years) demonstrated that the supplementation of seaweed fiber at 4 weeks significantly lowered the mean blood pressure by 10 mmHg ($p < 0.01$) on 12 g/day and by 11 mmHg on 24 g/day ($p < 0.01$) but not significantly lowered on 6 g/day seaweed fiber when compared with placebo treatment²⁹). However, since only 3.5% fiber intake came from seaweed in general Japanese population¹⁵), the inverse association between seaweed intake and risk of CVD mortality was unlikely due to total fiber intake *per se*.

Other possible mechanisms are the neuroprotective and antioxidant effects of seaweeds. Fucoxanthin, isolated from wakame powder, was dose-dependently attenuated neuronal cell after 4 day injury in the states of hypoxia and reoxygenation under an experimental ischemic model *in vitro*⁵). Fucoxanthin also shows stronger antioxidant activity than that of other carotenoids such as α -tocopherol³⁰).

Our study has several strengths. First, the JACC study is a large, nationwide, community-based prospective cohort study with almost complete follow-up, which allowed us to examine the associations of seaweed intake with mortality from CVD for the first time. Second, as a confounder, our study adapted to education, one of the key socioeconomic factors. Third, because of the wider distribution of seaweed intake in Japan than in Western countries, we were able to test the potential effect of regular seaweed intake, which has hardly been studied in Western populations.

However, some limitations of the present study warrant discussion. First, seaweed intake may be a reflection of healthy dietary patterns. Previous factor analysis in the JACC study identified seaweed intake consisted of a "vegetable" (healthy) pattern that included fresh fish, vegetables, fungi, potatoes, tofu (soybean curd), and fruits³¹). Among these foods, fungi, potatoes, and tofu were not adjusted in our

analysis, because these intakes were not confounded for the association with mortality from cerebral infarction. Second, the frequency of seaweed intake was evaluated only once, at baseline, although the validity and reproducibility of seaweed intake in this food frequency questionnaire were reasonably good (Spearman correlation coefficients of validity = 0.49, reproducibility = 0.66)²²). Thus, we did not consider changes in seaweed intake and cannot elucidate potential misclassification due to lifestyle and dietary change during the follow-up. Third, although the FFQ was moderately and was suitable to assess the categories of food and nutrient intakes but not to assess these amounts²²). Fourth, we used the mortality data, but not the incidence data as endpoints, which biased toward severe types of CVD and is also liable to misclassification. As for stroke, however, the widespread use of computed tomography scans since the 1980s, even in local hospitals, made the death certificate diagnosis of total stroke and stroke types sufficiently accurate³²). As for CHD, approximately one-quarter of deaths from CHD as recorded on death certificates were misdiagnosed^{25, 26}) so that the association between seaweed intake and mortality from CHD might be underestimated. The JACC study has shown that the associations dietary intakes of major nutrients and foods with CVD mortality³³⁻³⁵), which were similar to the previous findings from cohort studies with the incidence data³⁶⁻³⁸).

Conclusion

The present study revealed that seaweed intake was associated with reduced risk of mortality from total CVD and total stroke, especially cerebral infarction among Japanese men and women.

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