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Fish and Shellfish Consumption in Relation to Death from Myocardial Infarction among Men in Shanghai, China

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Between 1986 and 1989, 18,244 men aged 45–64 years in Shanghai, China, participated in a prospective study of diet and cancer. All participants completed an in-person, structured interview and provided blood and urine samples. As of September 1, 1998, 113 deaths from acute myocardial infarction were identified. After analyses were adjusted for age, total energy intake, and known cardiovascular disease risk factors, men who consumed ≥200 g of fish/shellfish per week had a relative risk of 0.41 (95% confidence interval: 0.22, 0.78) for fatal acute myocardial infarction compared with men consuming <50 g per week. Similarly, dietary intake of n-3 fatty acids derived from seafood also was significantly associated with reduced mortality from myocardial infarction. Neither dietary seafood nor n-3 fatty acid intake was associated with a reduced risk of death from stroke or ischemic heart disease other than acute myocardial infarction. However, approximately a 20% reduction in total mortality associated with weekly fish/shellfish intake was observed in the study population (relative risk = 0.79, 95% confidence interval: 0.69, 0.91). These prospective data suggest that eating fish and shellfish weekly reduces the risk of fatal myocardial infarction in middle-aged and older men in Shanghai, China. *Am J Epidemiol* 2001;154:809–16.

cerebrovascular accident; diet; fatty acids; fishes; myocardial ischemia; shellfish

High consumption of fish or n-3 fatty acids from seafood has been linked to low mortality from coronary heart disease in Greenland Eskimos (1). This observation has stimulated considerable research to test the hypothesis that consumption of fish or n-3 fatty acids reduces coronary heart disease mortality. Most epidemiologic studies of fish intake and cardiovascular disease to date have been conducted in Occidental populations. Intake levels have been generally low in these populations. Only about 14 percent of men in the United States eat more than one serving of fish per week (2), whereas about 50 percent of Chinese men in Shanghai report a similar consumption frequency. Distinct differences exist in circulatory disease profiles between Chinese and White men. In the United States, 1996 age-adjusted mortality rates (per 100,000 person-years) for coronary heart disease and stroke in men aged 35–74 years were 224 (21 percent of total mortality) and 44 (4 percent of total mortality), respectively (3). The corresponding figures for men in China were 100 (9 percent of total mortality) and 251 (23 percent of total mortality) (3). This paper describes, for the first known time, the relations between dietary seafood or n-3 fatty acid intake and mortality from vascular disease and all causes in a Chinese population.

MATERIALS AND METHODS

Study population

Between January 1, 1986, and September 30, 1989, we invited all eligible male residents of four small, geographically defined communities in a wide area of the city of Shanghai, China, to participate in a prospective epidemiologic study of diet and cancer (4). The eligibility criteria were age 45–64 years and no history of cancer. At recruitment, we interviewed each subject by using a structured questionnaire that asked for information on level of education, usual occupation, adult height and usual adult weight, history of tobacco use and alcohol consumption, current diet, and medical history. In addition to the interview, we collected a 10-ml nonfasting blood sample and a single-void urine sample from each study participant. Two sets of serum specimens were stored at –70°C and at –20°C, and urine samples were stored at –20°C only. During the 3-year recruitment period, 18,244 men (about 80 percent of eligible subjects) enrolled in the study. The study was approved by the institutional review boards of the University of Southern California (Los Angeles, California) and the Shanghai Cancer Institute (Shanghai, People's Republic of China).

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Abbreviations: CI, confidence interval; HDL, high density lipoprotein; ICD-9, *International Classification of Diseases,* Ninth Revision; RR, relative risk.

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Dietary assessment

At recruitment, specially trained nurses conducted in-person interviews. Each subject was asked to indicate the usual frequency (in number of times per day, per week, per month, or per year) of consumption of each of 45 food groups/items during the last 12 months (refer to Ross et al. (5) for the list of these food items). For seasonal foods, we obtained frequencies of consumption when the foods were in season. For example, in the early 1980s, tangerines were available in Shanghai only during the months of September to March. Thus, we asked subjects to indicate how frequently they consumed tangerines during September–March. The 45 food groups/items listed in the questionnaire included all common foods consumed in Shanghai. This food frequency questionnaire was subsequently validated by a series of 24-hour dietary recall interviews conducted in a randomly chosen subgroup (n = 432) of cohort subjects during April–May 1992 (unpublished data). Data from this 24-hour dietary recall substudy were also used to construct the standard portion weight for each food item in the food frequency questionnaire. Specifically, the median weight of all recorded servings was taken as the standard portion weight. Daily nutritive and nonnutritive intakes per subject were computed by using the Singapore Food Composition Table (6), which provides the nutrient values of cooked foods commonly consumed by the Chinese population, including those in Shanghai.

The food frequency questionnaire listed three seafood items—fresh fish, salted fish, and shellfish. The fresh fish commonly eaten in Shanghai include carp, beam, and pomfret. For salted fish, the common species are yellow croaker and hairtail. Similarly, the common shellfish in Shanghai are shrimp and crab. The standard portion weight (without bone) for fresh fish was determined to be 46.8 g. The corresponding figures for salted fish and shellfish were 25.9 g and 43.3 g. We calculated the average daily intake of fish and shellfish per subject by summing over the three seafood items, the cross-products of intake frequency, and standard portion weight. Daily intake of n-3 fatty acids from fish and shellfish was estimated by multiplying the daily amount of each seafood item by the corresponding n-3 fatty acid content (6): fresh fish, 0.57 g per 100 g; salted fish, 0.44 g per 100 g; and shellfish, 0.36 g per 100 g. Warm-water fish from the South China Sea (i.e., those available in Shanghai) are comparable in their fat content, which is low relative to that of cold-water species (such as salmon) commonly consumed in the United States (6).

Serum cholesterol measurements

Baseline serum cholesterol measurements were performed on all cases and their matched controls included in the present study. Cases consisted of 197 subjects who had died from ischemic heart disease by September 1, 1998. For each case with fatal ischemic heart disease, five controls matched to the index case by age (within 2 years), month and year of sample collection, and neighborhood of residence at recruitment were randomly chosen among cohort members who were alive on the date that the index case died.

The serum specimens stored at –20°C were used for cholesterol measurements, which were performed in the lipid laboratory of the Cardiovascular Disease Institute of Shanghai using standard methods (7). Total cholesterol, high density lipoprotein (HDL) cholesterol, and triglycerides were measured by using the enzymatic, colorimetric method. Low density lipoprotein cholesterol was calculated according to the Friedewald et al. formula (8).

Follow-up

Details of the follow-up procedures for this cohort have been described previously (4). Briefly, death certificates are routinely ascertained and matched against the cohort master file. In addition, all surviving cohort members are interviewed in person or by telephone annually. In terms of mortality, follow-up is essentially complete (99 percent). As of September 1, 1998, only 207 (1 percent) cohort members had been lost to follow-up. Among the 15,903 surviving members, only 223 (1.4 percent) had moved away from Shanghai and were followed by mail or telephone.

Endpoints

Causes of deaths (abstracted from death certificates) were systematically coded according to the *International Classification of Diseases,* Ninth Revision (ICD-9) by a retired nurse with special training. The specific endpoints of this study were deaths from acute myocardial infarction that included sudden and nonsudden cardiac death within 28 days (ICD-9 code 410), ischemic heart disease other than acute myocardial infarction (ICD-9 codes 411–414), and stroke (ICD-9 codes 430–438). The hospital records and other supporting medical documents for all cardiovascular deaths among cohort members were systematically reviewed; no evidence was found of other, more probable causes of death in these subjects.

Statistical analysis

For each subject, follow-up time was counted from the date of recruitment to September 1, 1998, or the date of death or loss to follow-up, whichever occurred first. For dietary seafood intake, study subjects were grouped into five categories of fish and shellfish consumption per week: <50, 50–<100, 100–<150, 150–<200, and ≥200 g, approximately equivalent to <1, 1, 2, 3, and ≥4 servings of seafood per week, respectively. For per-week intake of n-3 fatty acids from fish and shellfish, study subjects were categorized into equal quintiles: <0.27, 0.27–0.43, 0.44–0.72, 0.73–1.09, and ≥1.10 g.

The contingency table and one-way analysis of variance methods were used to examine the associations between fish and shellfish intake and various baseline characteristics of study subjects. Relative risks for subgroups of vascular disease mortality were computed for categories of dietary seafood and n-3 fatty acid intakes by using Cox proportional hazards models (9). Potential confounders included in the multivariate Cox proportional hazards models were age (years), level of education (primary school or less, middle school or higher), body mass index (<18.5, 18.5–<21.0, 21.0–<23.5, 23.5–<26.0, ≥26.0 kg/m^2), current smoker at recruitment (no, yes), average number of cigarettes smoked per day (continuous), number of alcoholic drinks consumed per week (none, 1–14, 15–28, ≥29), history of diabetes (no, yes), history of hypertension (no, yes), and total energy intake (kcal per day) (5, 10–12). The 95 percent confidence interval and two-sided p value were calculated for each relative risk.

Serum lipid measurements were available for only those subjects who died from ischemic heart disease and their matched controls. Standard matched-set methods (13) were used to examine the associations between dietary intake of fish and shellfish (or n-3 fatty acid) and ischemic heart disease mortality after further adjustment for the ratio of serum total cholesterol to HDL cholesterol.

Statistical testing for linear trends of various disease mortality associated with dietary fish/shellfish (or n-3 fatty acid) intake was based on ordinal values. Statistical computing was performed by using SAS version 6.12 (SAS Institute, Inc., Cary, North Carolina) and Epilog Windows version (Epicenter Software, Pasadena, California) statistical software packages. All p values quoted in this paper are two-sided.

RESULTS

Characteristics at baseline

Of the 18,244 cohort participants, 21 percent (n = 3,789) reported eating <50 g of fish/shellfish per week, including 143 (0.8 percent) who ate no seafood at all. Sixteen percent (n = 2,936) of the subjects consumed ≥200 g (equivalent to about ≥4 servings) of fish/shellfish per week. For all study subjects, the average intake of seafood was 129.1 g per week (table 1). There was no statistically significant difference in age or body mass index (kg/m^2) across various categories of fish/shellfish intake. Consumption of fish/shellfish was positively associated with level of education (p = 0.001), cigarette smoking (p =0.001), and alcohol drinking (p = 0.001). Men with a history of diabetes or hypertension consumed slightly more fish and shellfish than those without such a history (table 1).

Follow-up

As of September 1, 1998, the 18,244 cohort participants had contributed 179,466 person-years of follow-up. During the 12 years of follow-up, 2,134 deaths occurred (1,189 per 100,000 person-years). Nine percent of the subjects died from ischemic heart disease (n = 187, 104 per 100,000 per-

TABLE 1. Distributions of selected characteristics of cohort participants at baseline, according to dietary seafood intake, Shanghai Cohort Study, Shanghai, China, 1986–1998

Characteristic	Seafood intake (g/week)					Total cohort
	<50	50–<100	100–<150	150–<200	≥200	
Mean fish/shellfish intake (g/week)	29.3	76.2	124.2	176.8	321.9	129.1
Mean n-3 fatty acid intake (g/week)	0.15	0.38	0.65	0.91	1.66	0.66
No. of men	3,789	5,613	3,300	2,606	2,936	18,244
Mean age (years)	55.8	55.6	55.6	55.8	56.2	55.8
Mean body mass index (kg/m^2)	22.1	22.1	22.2	22.3	22.2	22.2
Level of education (%)						
Primary school or less	34	27	28	26	28	28
Middle school	44	47	47	48	49	47
College or higher	22	26	25	26	23	25
Smoking status (%)						
Current smoker						
<20 cigarettes/day	25	26	25	25	26	25
≥20 cigarettes/day	24	23	26	26	29	25
Past smoker	7	6	7	7	7	7
Never smoker	44	45	43	42	38	43
Alcohol consumption (%)						
None	65	61	55	54	47	57
1–14 drinks/week	20	23	26	25	26	24
15–28 drinks/week	9	10	12	13	16	12
≥29 drinks/week	6	6	6	8	11	7
Reported diagnosis of (%)						
Diabetes	1.2	1.2	1.2	1.2	1.6	1.3
Hypertension	23.4	24.4	24.7	24.8	26.4	24.6

son-years), 22 percent from stroke (n = 480, 267 per 100,000 person-years), and 41 percent from cancer (n = 865, 482 per 100,000 person-years).

Death from acute myocardial infarction

A total of 113 cohort members died from acute myocardial infarction during follow-up (63 per 100,000 person-years). Increasing level of dietary fish and shellfish intake was statistically significantly associated with a reduced risk of fatal myocardial infarction (p for trend = 0.04). Adjustment for known cardiovascular risk factors did not materially alter this inverse association (p for trend = 0.03). Men who consumed ≥200 g of fish/shellfish per week (≥4 servings per week) experienced a 59 percent reduction in myocardial infarction mortality (adjusted relative risk (RR) = 0.41, 95 percent confidence interval (CI): 0.22, 0.78) relative to those who ate <50 g of seafood per week (table 2).

Men who ate ≥50 g (≥1 serving) of fish/shellfish per week had a 44 percent reduced risk of fatal myocardial infarction (adjusted RR = 0.56, 95 percent CI: 0.37, 0.85) compared with those who ate less. There was no evidence of a further reduction in myocardial infarction mortality with a fish/shellfish intake level of more than one serving per week (p = 0.97 for trend in risk between men in the 50–<100 g to ≥200 g categories of fish intake per week).

Of the three seafood items specifically listed in the questionnaire, fresh fish (86.3 g per week) accounted for 67 percent of total seafood consumption; shellfish (38.6 g per week) and salted fish (4.2 g per day) accounted for 30 and 3 percent, respectively. In analyses conducted separately for fish and shellfish, the inverse associations with acute myocardial infarction were statistically significant for both fresh/salted fish intake and shellfish intake (p for trend = 0.02 in both instances) (table 2).

Average intake of n-3 fatty acids from fish and shellfish in this cohort was estimated to be 0.66 g per week (table 1). Table 3 presents the associations between intake of n-3 fatty acids from seafood and categories of vascular disease mortality. Similar to the relations with seafood intake, fatal myocardial infarction was inversely associated with consumption of n-3 fatty acids derived from fish and shellfish. Compared with men in the lowest 20 percent of n-3 fatty acid intake (<0.27 g per week), those who consumed higher levels had a significantly reduced risk of fatal myocardial infarction (RR = 0.55, 95 percent CI: 0.37, 0.83). Adjustment for known cardiovascular disease risk factors did not alter the inverse association (p for trend = 0.02 after adjustment) (table 3).

Early symptoms of cardiovascular disease could result in changes in dietary habits. Therefore, we repeated all data analyses described above and excluded all deaths and per-

TABLE 2. Relative risks of cardiovascular disease mortality, according to dietary seafood intake, Shanghai Cohort Study, Shanghai, China, 1986–1998

Seafood intake (g/week)	Person-years	Acute myocardial infarction (ICD-9* code 410)				Other ischemic heart disease (ICD-9 codes 411–414)				Stroke (ICD-9 codes 430–438)			
		No. of deaths	RR†	Multivariate RR‡	95% CI*	No. of deaths	RR†	Multivariate RR‡	95% CI	No. of deaths	RR†	Multivariate RR‡	95% CI
Fish/shellfish													
<50	36,892	33	1.00	1.00		17	1.00	1.00		101	1.00	1.00	
50–<100	55,115	28	0.56§	0.55	0.33, 0.91	24	0.93	0.87	0.47, 1.62	141	0.94	0.93	0.72, 1.21
100–<150	32,499	21	0.69	0.65	0.38, 1.14	9	0.58	0.54	0.24, 1.22	70	0.79	0.79	0.58, 1.07
150–<200	25,767	17	0.67	0.66	0.36, 1.19	12	0.97	0.92	0.43, 1.94	71	0.99	1.01	0.74, 1.37
≥200	29,194	14	0.44§	0.41	0.22, 0.78	12	0.76	0.68	0.32, 1.46	97	1.11	1.11	0.83, 1.47
p for trend			0.04	0.03			0.51	0.37			0.44	0.42	
Fish only													
<30	32,550	29	1.00	1.00		13	1.00	1.00		91	1.00	1.00	
30–<60	39,355	30	0.56§	0.54	0.32, 0.90	28	1.18	1.08	0.56, 2.10	142	0.86	0.84	0.64, 1.09
60–<100	39,992	28	0.74	0.72	0.42, 1.21	15	0.91	0.84	0.40, 1.77	99	0.88	0.87	0.65, 1.15
100–<150	24,293	16	0.65	0.63	0.34, 1.17	6	0.57	0.53	0.20, 1.40	68	0.95	0.95	0.69, 1.31
≥150	23,277	10	0.39§	0.35	0.17, 0.72	12	1.10	0.92	0.41, 2.06	80	1.12	1.05	0.77, 1.43
p for trend			0.048	0.02			0.55	0.34			0.36	0.47	
Shellfish only													
<10	63,301	52	1.00	1.00		30	1.00	1.00		183	1.00	1.00	
10–<30	34,519	18	0.67	0.65	0.38, 1.11	10	0.68	0.66	0.32, 1.35	80	0.87	0.86	0.66, 1.12
30–<60	50,210	28	0.68	0.66	0.42, 1.05	17	0.75	0.73	0.40, 1.34	128	0.93	0.96	0.77, 1.21
60–<100	20,505	11	0.62	0.64	0.33, 1.23	14	1.45	1.55	0.81, 2.96	59	1.01	1.08	0.81, 1.46
≥100	10,932	4	0.39	0.40	0.14, 1.12	3	0.56	0.58	0.17, 1.92	30	0.93	1.02	0.69, 1.51
p for trend			0.02	0.02			0.91	0.99			0.76	0.73	

* ICD-9, *International Classification of Diseases*, Ninth Revision; CI, confidence interval.

† RR, relative risk adjusted for age (years) and total energy intake (calories/day).

‡ In addition to age (years) and total energy intake (calories/day), the multivariate Cox proportional hazards model included level of education (primary school or less, middle school or higher), body mass index (<18.5, 18.5–<21, 21–<23.5, 23.5–<26, ≥26 kg/m^2), current smoker at recruitment (no, yes), average no. of cigarettes smoked per day (continuous), no. of alcoholic drinks consumed per week (none, 1–14, 15–28, ≥29), history of diabetes (no, yes), and history of hypertension (no, yes).

§ Two-sided p < 0.05, test for RR = 1.0.

TABLE 3. Relative risks of cardiovascular disease mortality, according to dietary intake of n-3 fatty acids from seafood, Shanghai Cohort Study, Shanghai, China, 1986–1998

Intake of n-3 fatty acids in quintiles (g/week)	Person-years	Acute myocardial infarction (ICD-9* code 410)				Other ischemic heart disease (ICD-9 codes 411–414)				Stroke (ICD-9 codes 430–438)			
		No. of deaths	RR†	Multivariate RR‡	95% CI*	No. of deaths	RR†	Multivariate RR‡	95% CI	No. of deaths	RR†	Multivariate RR‡	95% CI
<0.27	35,583	33	1.00	1.00		15	1.00	1.00		106	1.00	1.00	
0.27–0.43	32,076	12	0.39§	0.39	0.20, 0.75	12	0.86	0.82	0.38, 1.75	75	0.78	0.76	0.57, 1.03
0.44–0.72	54,769	37	0.70	0.67	0.42, 1.08	21	0.89	0.83	0.42, 1.61	124	0.76¶	0.76	0.58, 0.98
0.73–1.09	28,613	16	0.54¶	0.53	0.29, 0.97	15	1.17	1.11	0.54, 2.30	81	0.92	0.93	0.69, 1.24
≥1.10	28,425	15	0.47¶	0.43	0.23, 0.81	11	0.80	0.71	0.32, 1.57	94	1.01	1.00	0.75, 1.33
p for trend			0.04	0.02			0.88	0.68			0.70	0.36	

* ICD-9, *International Classification of Diseases*, Ninth Revision; CI, confidence interval.

† RR, relative risk adjusted for age (years) and total energy intake (calories/day).

‡ In addition to age (years) and total energy intake (calories/day), the multivariate Cox proportional hazards model included level of education (primary school or less, middle school or higher), body mass index (<18.5, 18.5–<21, 21–<23.5, 23.5–<26, ≥26 kg/m²), current smoker at recruitment (no, yes), average no. of cigarettes smoked per day (continuous), no. of alcoholic drinks consumed per week (none, 1–14, 15–28, ≥29), history of diabetes (no, yes), and history of hypertension (no, yes).

§ Two-sided $p < 0.01$, test for RR = 1.0.

¶ Two-sided $p < 0.05$, test for RR = 1.0.

son-year contributions from the cohort during the first 2 years of follow-up. Results were similar.

We further examined the relations between seafood or n-3 fatty acid intake and mortality from acute myocardial infarction, taking into consideration the intake levels of red meats; poultry; vegetables; fruit; soybeans and soy products; legumes; carbohydrate; protein; total fat; saturated, monounsaturated, and polyunsaturated fats other than n-3 fatty acids; and cholesterol. Separate inclusion of these dietary variables in multivariate models did not materially alter the associations of fish/shellfish or n-3 fatty acid intake with fatal myocardial infarction.

We reexamined the association between seafood (or n-3 fatty acid) intake and myocardial infarction mortality after adjustment for the ratio of baseline serum total cholesterol to HDL cholesterol. Baseline serum measurements of total and HDL cholesterol were available for only 99 subjects who died from myocardial infarction and from their 447 matched controls. Ten percent ($n = 10$) of cases and 5 percent ($n = 24$) of controls had baseline serum total cholesterol levels higher than 240 mg/dl. Adjustment for the ratio of total cholesterol to HDL cholesterol did not materially alter the inverse association between seafood (or n-3 fatty acid) intake and myocardial infarction mortality.

Death from other vascular disease

Seventy-four deaths from ischemic heart disease other than acute myocardial infarction were identified during follow-up (41 per 100,000 person-years). In contrast to the inverse relation with acute myocardial infarction mortality, neither fish/shellfish intake nor n-3 fatty acid intake from seafood was associated with mortality from other forms of ischemic heart disease (tables 2 and 3). Adjustment for known cardiovascular disease risk factors or the ratio of serum total to HDL cholesterol did not materially change these associations.

Consumption of fish and shellfish was not related to stroke mortality. Men who ate ≥200 g of seafood per week had a fatal stroke risk similar to those who ate <50 g of seafood per week (table 2). Similarly, there was no evidence that a high level of intake of n-3 fatty acids from seafood was associated with stroke mortality (table 3). Adjustment for known cardiovascular disease risk factors did not materially change the associations between seafood or n-3 fatty acid intake and stroke mortality.

Total mortality

Compared with men who consumed <50 g of fish/shellfish per week, those who consumed more had an approximately 20 percent reduction in total mortality. Adjustment for cardiovascular disease risk factors did not materially change the association. After deaths from acute myocardial infarction were excluded from total mortality, the inverse association with seafood (or n-3 fatty acid) intake remained (table 4).

DISCUSSION

To our knowledge, the current study is the first prospective investigation of the role of dietary fish and shellfish in cardiovascular disease mortality in the Chinese population. We noted that middle-aged or older men in Shanghai, China, who consumed at least one serving of fish and shellfish per week had a 44 percent reduced risk of fatal myocardial infarction compared with less-frequent consumers.

The current study has a number of strengths. Among them are the following: 1) the prospective study design, eliminating the possibility of recall bias; 2) adjustment for various known cardiovascular disease risk factors at baseline, including serum total/HDL cholesterol ratio, obesity, hypertension, cigarette smoking, and alcohol drinking, thus minimizing potential confounding effects; 3) virtually complete follow-up (only 1 percent of cohort members were lost to follow-up), minimizing the possibility of selection bias; 4) the relatively long follow-up period, minimizing the impact

TABLE 4. Relative risks of total mortality, according to dietary seafood intake, Shanghai Cohort Study, Shanghai, China, 1986–1998

Seafood intake (g/week)	Person-years	Total mortality				Total mortality excluding acute myocardial infarction			
		No. of deaths	RR*	Multi-variate RR†	95% CI‡	No. of deaths	RR*	Multi-variate RR†	95% CI
<50	36,892	520	1.00	1.00		487	1.00	1.00	
50–<100	55,115	602	0.77§	0.79	0.70, 0.89	574	0.79§	0.81	0.72, 0.91
100–<150	32,499	343	0.74§	0.76	0.66, 0.87	322	0.74§	0.76	0.66, 0.88
150–<200	25,767	313	0.83§	0.86	0.75, 0.99	296	0.84¶	0.88	0.76, 1.02
≥200	29,194	356	0.77§	0.79	0.69, 0.91	342	0.80§	0.82	0.71, 0.95
p for trend			0.003	0.01			0.01	0.04	

* RR, relative risk adjusted for age (years) and total energy intake (calories/day).

† In addition to age (years) and total energy intake (calories/day), the multivariate Cox proportional hazards model included level of education (primary school or less, middle school or higher), body mass index (<18.5, 18.5–<21, 21–<23.5, 23.5–<26, ≥26 kg/m^2), current smoker at recruitment (no, yes), average no. of cigarettes smoked per day (continuous), no. of alcoholic drinks consumed per week (none, 1–14, 15–28, ≥29), history of diabetes (no, yes), and history of hypertension (no, yes).

‡ CI, confidence interval.

§ Two-sided $p < 0.01$, test for RR = 1.0.

¶ Two-sided $p < 0.05$, test for RR = 1.0.

of recent changes in diet due to symptoms of disease; and 5) the distinct dietary habits (eating fish more often but eating smaller portions per meal) of US populations, thus increasing the informativeness of the study database in testing the study hypothesis.

Our study has several limitations. The principal one is reliance on death certificates as the sole diagnostic source of cardiovascular disease mortality information. However, we reviewed the hospital records and other supporting medical documents for all cardiovascular deaths of cohort members and found no evidence of other, more probable causes of death in these subjects. Concerning ischemic heart disease deaths, 67 percent of the patients had been hospitalized for the same disease prior to death, and, for an additional 16 percent of the patients, their death certificates were signed by an attending physician at a major medical center. The corresponding figures for stroke death were 85 and 9 percent. Another important limitation of the study is the single measure of fish consumption and therefore the inability to account for changes in intake over time. Other limitations include the relatively small sample size of myocardial infarction deaths, resulting in the estimates of relative risks with relatively wide confidence intervals, and the absence of women in the study population.

As with any observational epidemiologic study, the inverse association we found between fish/shellfish consumption and fatal myocardial infarction could be due, at least in part, to residual confounding. High levels of consumption of fish and shellfish may be a marker of a healthy lifestyle. We examined the association between dietary fish/shellfish consumption and myocardial infarction mortality after adjustment for various indices of diet and other lifestyle factors, and no substantial changes were observed. The inverse fish-myocardial infarction association remained after further adjustment for the ratio of baseline serum total to HDL cholesterol. Actually, in this population, fish intake was higher in subjects with histories of diabetes and hypertension, conditions that are established risk factors for coronary heart disease. As expected, adjustment for these two medical conditions in multivariate analyses led to a stronger inverse association between fish and myocardial infarction.

The finding that moderate amounts of fish can protect against fatal myocardial infarction in Chinese men is consistent with previous observations in Occidental populations. In a case-control study in the United States, Siscovick et al. reported a greater than 50 percent reduction in the risk of primary cardiac arrest associated with high consumption levels of dietary n-3 fatty acids or high levels of n-3 fatty acids in red blood cell membranes (14). One ecologic study in Japan reported that coronary heart disease mortality was lower in residents of a fishing village than in those of a farming village (15). Four cohort studies have examined the relation of dietary fish (or n-3 fatty acid from fish) with fatal myocardial infarction (16–19), and three found a statistically significant, inverse association (16–18). Eight other cohort studies have investigated the association between fish (or n-3 fatty acid) intake and coronary heart disease (including myocardial infarction) mortality (20–27); four found a statistically significant, inverse association (20–23). Four cohort studies have examined the association between fish (or n-3 fatty acid) intake and nonfatal myocardial infarction (17, 24, 25, 28), but none found a statistically significant association. The Diet and Reinfarction Trial (29) randomized 2,033 men after a first myocardial infarction into two groups—one received advice to eat at least two portions of fatty fish per week, and the other did not. At the end of the 2-year study period, total mortality in the intervention group was significantly reduced by 29 percent (mainly because of a reduction in coronary heart disease mortality); however, there was no difference in myocardial reinfarction incidence. The authors hypothesized that fish consumption may reduce the risk of fatal arrhythmia and therefore mortality from myocardial infarction without affecting the incidence of recurrent myocardial infarction

(29). An intervention trial in Italy has shown similar results; myocardial infarction survivors receiving approximately 1 g of eicosapentaenoic and docosahexaenoic acids (n-3 fatty acids from fish) per day for 3.5 years experienced a statistically significant 14 percent reduction in total mortality and a 17 percent reduction in cardiovascular disease mortality (30).

Our data are compatible with this arrhythmia hypothesis, which would predict a stronger protective effect of fish against fatal myocardial infarction for cohort subjects whose dietary information is obtained relatively close to the occurrence of a fatal myocardial infarction (i.e., information on recent intake is more relevant than intake data obtained years prior to clinical outcome). Indeed, for men whose fatal myocardial infarction occurred within the 5 years of study enrollment, the relative risk was 0.48 (95 percent CI: 0.25, 0.91) for those who ate ≥50 g of seafood per week relative to those consuming less. The comparable figure for subjects whose fatal myocardial infarction occurred more than 5 years postenrollment was 0.63 (95 percent CI: 0.36, 1.07).

Experimental data also suggest that fish oil may have antiarrhythmic properties and thus can reduce vulnerability to life-threatening arrhythmias during cardiac ischemia. In animal experiments, a diet supplemented with tuna fish oil significantly reduces the incidence and severity of arrhythmia and prevents ventricular fibrillation following coronary occlusion and reperfusion in rats (31). Infusion of n-3 fatty acids prevents ischemia-induced ventricular fibrillation in dogs known to be susceptible to sudden death (32). Adult marmoset monkeys fed a diet supplemented with tuna fish oil show a statistically significant elevation in their ventricular fibrillation threshold before or after acute coronary artery occlusion (33). In human experiments, myocardial infarction survivors receiving 5.2 g of eicosapentaenoic and docosahexaenoic acids per day for 12 weeks demonstrated a statistically significantly increased heart rate variability relative to 1) their baseline values before treatment and 2) comparable controls (34). Consumption of as little as one serving of fish per week, the threshold level for protection in this study, is associated with an increase in heart rate variability (35), which relates to a lower risk of arrhythmic death after myocardial infarction (36). Data from both the current study and the Physicians' Health Study (17) are consistent with the notion that the amount of n-3 fatty acids (and/or other unidentified constituents) contained in one serving of fish consumed at a weekly interval is sufficient to protect against arrhythmia in persons at risk for myocardial infarction, thereby reducing the risk of fatal myocardial infarction.

Our study did not show a significant benefit on mortality from ischemic heart disease other than acute myocardial infarction. This negative finding is consistent with that from the Western Electric study (16), the only known study that has examined this particular association.

Two prospective cohort studies have examined the relation between fish intake and stroke death (2, 28). Data from the First National Health and Nutrition Examination Survey (NHANES I) indicated that fish intake was associated with a reduced risk of stroke death in White women as well as Black men and women, but not in White men (2). The Physicians' Health Study did not show a relation between fish intake and stroke death (28). If the protective effect of n-3 fatty acids on fatal myocardial infarction is mediated via antiarrhythmic properties, then lack of an association between fish (or n-3 fatty acid) intake and stroke death is not surprising.

Consistent with results from the Physicians' Health Study (17), the present data demonstrated an inverse association between seafood consumption and total mortality. Persons who consume more seafood might have healthier lifestyles than those who consume less seafood. Thus, the reduced total mortality in frequent consumers of seafood may merely reflect other unmeasured protective lifestyle factors associated with fish intake. This possibility is not likely in our study population. We actually found higher fish intake among subjects with histories of diabetes and hypertension. Alternatively, the inverse association between seafood consumption and mortality from causes other than acute myocardial infarction may suggest that fish/shellfish or n-3 fatty acids (or other unidentified constituents) in seafood can have beneficial effects on noncardiac deaths. N-3 fatty acids from fish have been found to have anti-inflammatory and anti-asthmatic effects (37, 38). Epidemiologic data suggest that fish or n-3 fatty acid consumption also has a beneficial effect on certain types of cancer (21, 39). Although the cause is presently unclear, the observed protective effect of fish consumption on total mortality is both reassuring and intriguing, and it warrants further study.

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