Original Contributions

Fish Consumption and Risk of Sudden Cardiac Death

Christine M. Albert, MD; Charles H. Hennekens, MD; Christopher J. O'Donnell, MD; Umed A. Ajani, MBBS; Vincent J. Carey, PhD; Walter C. Willett, MD; Jeremy N. Ruskin, MD; JoAnn E. Manson, MD

Context.—Dietary fish intake has been associated with a reduced risk of fatal cardiac end points, but not with nonfatal end points. Dietary fish intake may have a selective benefit on fatal arrhythmias and therefore sudden cardiac death.

Objective.—To investigate prospectively the association between fish consumption and the risk of sudden cardiac death.

Design.—Prospective cohort study.

Setting.—The US Physicians' Health Study.

Patients.—A total of 20 551 US male physicians 40 to 84 years of age and free of myocardial infarction, cerebrovascular disease, and cancer at baseline who completed an abbreviated, semiquantitative food frequency questionnaire on fish consumption and were then followed up to 11 years.

Main Outcome Measure.—Incidence of sudden cardiac death (death within 1 hour of symptom onset) as ascertained by hospital records and reports of next of kin.

Results.—There were 133 sudden deaths over the course of the study. After controlling for age, randomized aspirin and beta carotene assignment, and coronary risk factors, dietary fish intake was associated with a reduced risk of sudden death, with an apparent threshold effect at a consumption level of 1 fish meal per week (P for trend=.03). For men who consumed fish at least once per week, the multivariate relative risk of sudden death was 0.48 (95% confidence interval, 0.24-0.96; P=.04) compared with men who consumed fish less than monthly. Estimated dietary n-3 fatty acid intake from seafood also was associated with a reduced risk of sudden death but without a significant trend across increasing categories of intake. Neither dietary fish consumption nor n-3 fatty acid intake was associated with a reduced risk of total myocardial infarction, nonsudden cardiac death, or total cardiovascular mortality. However, fish consumption was associated with a significantly reduced risk of total mortality.

Conclusion.—These prospective data suggest that consumption of fish at least once per week may reduce the risk of sudden cardiac death in men.

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SOME[1-6] but not all[7-10] prospective cohort studies of the association between fish consumption and cardiovascular mortality have reported inverse associations. In general, fish consumption has been associated with lower cardiac mortality in populations characterized by low fish intake in which a substantial proportion rarely or never consumed fish[1-6] and not in those with higher levels of fish intake.[7-10] Studies in which nonfatal coronary heart disease was examined have shown no relationship.[9,10] Randomized trial data are limited, but 1 secondary prevention trial showed an association between fish intake and reduction in cardiovascular mortality but not reinfarction.[11] Based on these results, it has been hypothesized that low levels of dietary fish intake may be unrelated to the incidence of myocardial infarction, but could reduce coronary disease mortality by decreasing fatal arrhythmias and therefore sudden cardiac death.[12]

Experimental data in dogs[13] and primates[14] suggest that the n-3 fatty acids in fish have antiarrhythmic properties. Further, a retrospective case-control study found that, when compared with no intake, n-3 fatty acid consumption equivalent to 1 fatty fish meal per week was associated with a 50% reduction in the risk of primary cardiac arrest,[15] suggesting that antiarrhythmic effects occur at the low levels of fish intake that have been associated with reduced coronary heart disease mortality. Contrary to these findings, no association was found between low levels of fish consumption and sudden death from myocardial infarction in a recent prospective study,[5] but a strong inverse association

was observed with nonsudden death from myocardial infarction as determined by death certificates. We addressed this controversy further by prospectively examining the association between fish consumption and sudden cardiac death ascertained from medical records and firsthand reports among male physicians enrolled in the Physicians' Health Study.

METHODS

The methods of the Physicians' Health Study have been described in detail elsewhere.[16,17] Briefly, 22 071 US male physicians who were 40 to 84 years old in 1982 and had no history of myocardial infarction, stroke, transient ischemic attack, or cancer (except nonmelanoma skin cancer) were assigned at random using a 2-by-2 factorial design to receive aspirin, beta carotene, both active drugs, or both placebos. At baseline, the physicians completed questions on health status and risk factors for cardiovascular disease, including alcohol and vitamin use, dietary intake of selected foods, and exercise. Information on cardiovascular events was updated every 6 months for the first year and annually thereafter through brief follow-up questionnaires. Dietary intakes of selected foods were ascertained by 2 abbreviated, semiquantitative food frequency questionnaires consisting of 20 items each[18] administered at 12 and 18 months. The 1988 (5-year follow-up) questionnaire inquired about current fish-oil supplement use, but not about dose, frequency, or length of use.

Assessment of Fish Consumption

At 12 months, respondents were asked separately to indicate how often, on aver-

age, they consumed 4 types of fish or shellfish: canned tuna fish; dark meat fish (eg, mackerel, salmon, sardines, bluefish, or swordfish), 84 to 112 g; other fish, 84 to 112 g; and shrimp, lobster, or scallops as a main dish. Seven response categories ranged from rarely/never to 2 or more per day. We calculated average daily intake by summing the frequencies of the 4 fish or shellfish items. The nutrient intake of marine n-3 fatty acids was estimated by multiplying the frequency of each item with the nutrient composition of the portion of seafood (tuna, 0.69 g; dark fish, 1.37 g; other fish, 0.17 g; and shellfish, 0.46 g) and summing over all items. Nutrient composition was based on US Department of Agriculture[19] and other food composition tables.[20]

Reproducibility and validity of the 4 questionnaire items on seafood intake were assessed in a study of 127 male health professionals aged 45 to 70 years.[21,22] The correlation between 2 administrations of the questionnaires 1 year apart ranged from 0.48 for fish to 0.67 for shellfish.[21] Validity of the questionnaire was assessed by comparing fish intake as reported on the questionnaire with fish intake ascertained from two 1-week dietary records obtained about 6 months apart (Spearman correlation coefficient=0.61; $P<.001$)[21] and by comparing the dietary intake of n-3 fatty acids estimated from the questionnaire to the percentage measured in adipose tissue of 118 of the 127 men (Spearman correlation coefficient=0.49; $P<.001$).[22]

End Point Definition

The ascertainment of cardiovascular disease events was by self-report on follow-up questionnaires, and deaths were generally reported by postal authorities or next of kin. All such events were reviewed by an end points committee of 4 physicians for confirmation by medical records obtained from hospitals and attending physicians. Records were reviewed for 95.6% of the myocardial infarctions and 94.8% of the deaths. The next of kin was interviewed regarding the circumstances surrounding the death if it was not adequately documented in the medical record. Cases of nonfatal myocardial infarction were confirmed with the use of the World Health Organization criteria[23]; all cases had documentation of symptoms and either electrocardiographic changes or elevated serum cardiac enzyme levels consistent with infarction. Silent myocardial infarctions were not included because they could not be dated accurately. All fatal myocardial infarctions were confirmed by hospital records or autopsy. Deaths due to a cardiovascular cause (*International Classification of Diseases, Ninth Revision* [*ICD-9*] codes 390-459) were confirmed by convincing evidence of a cardiovascular mechanism from all available

sources, including death certificates, hospital records, autopsy reports, symptoms, and circumstances of death. These deaths included cardiac, cerebrovascular, and vascular deaths. Deaths in which there was evidence of coronary heart disease at or prior to death and in which a noncoronary cause of death was not found were classified as coronary heart disease deaths (*ICD-9* codes 410-414). Deaths that occurred within 1 hour of the onset of symptoms were also classified as coronary heart disease deaths unless there was evidence to the contrary, because these deaths are primarily due to coronary heart disease in autopsy series. If a participant experienced a nonfatal myocardial infarction prior to death, both end points were included in the analyses.

To ascertain the specific end point of sudden cardiac death, medical records and reports from next of kin of all cardiovascular deaths (excluding strokes) were re-reviewed by 2 cardiologists unaware of exposure status, and agreement was reached. Sudden death was defined as death within 1 hour of symptom onset, a witnessed cardiac arrest, or both, or abrupt collapse not preceded by more than 1 hour of symptoms that precipitated the terminal event. Information from the death certificate was not used in the determination of the timing of death. To increase our specificity for arrhythmic death, we excluded any patient who had evidence of collapse of the circulation (hypotension, exacerbation of congestive heart failure, or altered mental status) prior to the disappearance of the pulse. Finally, no other probable cause of death other than cardiac was suggested by history or autopsy.

Unwitnessed deaths with no information on timing but with an autopsy consistent with arrhythmic cardiac death (ie, acute coronary thrombosis or severe coronary artery disease without myocardial necrosis or other pathologic findings to explain death) were considered possible sudden cardiac deaths, and the analysis was performed both including and excluding these deaths. Nonsudden cardiac deaths were defined as deaths in which the length of symptoms prior to death was greater than 1 hour. Deaths (often unwitnessed) in which the timing could not be determined accurately from the available information were not classified.

Study Population

We excluded 620 physicians who either died prior to returning or failed to return the 12-month questionnaire or to answer 2 or more questions regarding fish consumption. To minimize misclassification in the lowest categories of dietary fish intake, we excluded 123 physicians who had missing information for 1 of the 4 seafood questions and responses of "rarely/

never" or "1-3 times per month" for the remaining 3. We also excluded 777 physicians who reported fish-oil supplement use on the 1988 questionnaire, because the focus of this study was on dietary intake, and the dose and the date of initiation of supplements were not known. These exclusions yielded a study population of 20 551. We did not exclude participants who developed evidence of cardiovascular disease during follow-up, but controlled for evidence of cardiovascular disease prior to the return of the 12-month questionnaire in the multivariate model because prior disease may have influenced fish consumption.

Data Analysis

Participants contributed follow-up time from the date of return of the 12-month questionnaire to date of death or to the scheduled end of the randomized beta carotene component of the study on December 31, 1995, whichever came first. To detect differences in relative risks (RRs) at low levels of fish intake, men who answered rarely/never to all 4 fish questions were used as the reference group for all analyses, and the fish consumers were categorized into 4 categories that emphasized the low levels of intake (1-3 meals per month, 1-2 meals per week, 2-5 meals per week, ≥5 meals per week) rather than equal quartiles. For n-3 fatty acid intake, the men who ate any fish were grouped into equal quartiles of intake and compared with the reference category who rarely or never ate fish.

Relative risks were computed using Cox proportional hazards models,[24] controlling for age and randomized aspirin and beta carotene assignment. A multivariate Cox proportional hazards model was used to control for potential confounders, including prior cardiovascular disease, body mass index, smoking status, history of diabetes, history of hypertension, history of hypercholesterolemia, alcohol consumption, vigorous exercise, and use of vitamin E, vitamin C, and multivitamins. Other dietary factors (red meat, vegetables, fruits, dairy, chicken or turkey, and fried foods) were tested individually for associations with sudden cardiac death in separate Cox models, and each was entered into the multivariate model to test for confounding. Tests for trend were performed by assigning an ordinal variable for each level of consumption and modeling this as a continuous variable in separate Cox proportional hazards models. For each RR, 2-sided P values and 95% confidence intervals (CIs) were calculated. The relationships between both fish intake and n-3 fatty acid intake and risk of sudden death were explored further using spline regression modeling. Restricted cubic spline models with 4 or 5 knots were used to flexibly model these

relationships using measured values of fish or n-3 fatty acid intake and avoiding the need for prior specification of the RR function or the location of a threshold exposure value.[25]

RESULTS

Of the 20 551 men included in this analysis, 637 (3.1%) reported rarely or never consuming fish, and 2212 (10.8%) reported consuming fish at least 5 times weekly. Most (80%) consumed fish between 1 and 4 times per week, and the mean level of consumption was 2.5 meals per week. Dietary fish intake and n-3 fatty acid intake were associated with several coronary risk factors (Table 1). Men who consumed more fish tended to be at higher risk because of a history of high cholesterol levels or hypertension or a family history of coronary heart disease. However, they were also more likely to exercise vigorously at least once per week and use antioxidant vitamin supplements. Fish intake was also directly or indirectly associated with a variety of dietary factors (Table 1). We therefore analyzed the relation of fish consumption (and n-3 fatty acid intake) to sudden death, with and without adjustment for all these variables.

Sudden Deaths

Over 11 years and 253 777 person-years of follow-up, 133 sudden deaths (115 definite and 18 probable) were documented. After adjustment for age and aspirin and beta carotene assignment, fish consumption was inversely related to the risk of sudden cardiac death (Table 2) with a significant trend ($P=.03$) across 5 levels of dietary fish consumption. Compared with men who ate fish less than once per month, the age-adjusted RR of sudden death for those who consumed fish in any amount was consistently reduced. This inverse association reached significance at a consumption level of between 1 and 2 servings of fish per week with an RR of 0.42 ($P=.02$), with minimal change in this reduction at higher levels of consumption. When men who ate fish at least once per week were analyzed together in a secondary analysis, the trend across the 3 categories was more extreme (uncorrected $P=.006$; significant after Bonferroni correction, $P=.04$) (Table 2).

After further adjustment for coronary risk factors and prior cardiovascular disease, these relationships were not substantially altered, except the P for trend was no longer significant across 5 fish categories but remained significant across 3 (number of fish meals <1 per month, 1-3 per month, ≥1 per week), compatible with a possible threshold effect at 1 fish meal per week. However, the test for trend across the 3 categories would be judged of borderline significance after Bonferroni correction for the 6 possible ways to retabulate the prior 5 categories (significance criterion, $P=.008$). A smooth model of the relationship between number of fish meals per week as a continuous function and the relative hazard of sudden cardiac death after multivariate adjustment is shown in Figure 1. This model uses average daily fish intake and permits risk comparison across low exposures without arbitrary categorization or selection of a priori threshold values. A similar relationship suggesting a threshold effect was found, but the CIs were wide.

All other food groups tested individually (red meat, chicken, vegetables, fruits,

Table 1.—Relationship of Dietary Fish Intake at 12 Months to Coronary Heart Disease Risk Factors at Baseline*

Variable	Average Frequency of Dietary Fish Intake†					Total Cohort
	<1 Time per mo	1-3 Times per mo	1-<2 Times per wk	2-<5 Times per wk	≥5 Times per wk	
No. of men	637	1262	6443	9997	2212	20 551
Age, mean, y	53.7	53.4	53.1	53.2	52.9	53.2
Smoking status						
Current						
≥20 cigarettes per d	6.9	9.1	8.5	6.3	5.5	7.1
<20 cigarettes per d	4.3	4.7	4.0	3.9	2.5	3.9
Past	30.6	35.5	38.2	41.0	39.8	39.2
Never	58.2	50.7	49.3	48.7	52.2	49.5
Alcohol use						
Rarely	39.7	22.6	16.9	11.4	11.0	14.7
Monthly	10.9	13.9	12.0	10.5	9.8	11.2
Weekly	32.0	42.8	46.9	51.9	53.4	49.3
Daily	17.3	20.7	24.1	26.2	24.9	24.8
Reported diagnosis of						
Diabetes	3.9	2.9	2.3	2.2	2.4	2.4
High cholesterol	3.3	3.8	5.4	6.3	6.9	5.8
Hypertension	12.4	13.7	13.1	13.7	15.9	13.6
Vigorous exercise ≥1 time per wk	67.8	67.1	69.9	73.9	75.3	71.6
Body mass index, mean, kg/m^2	24.7	24.7	25.0	25.0	24.9	24.9
Parental history of myocardial infarction prior to age 60 y	12.1	11.7	12.6	13.1	15.5	13.1
Vitamin supplement use						
Vitamin E	9.3	9.3	7.6	10.2	13.5	9.6
Vitamin C	21.7	21.0	20.9	22.1	27.2	22.2
Multivitamin	36.3	33.5	34.3	34.8	38.3	34.9
Food intake, servings per wk‡						
Red meat	3.7	4.4	4.5	4.3	3.9	4.3
Chicken or turkey	1.2	1.5	1.7	2.0	2.7	1.9
Vegetables	8.9	8.3	9.1	10.8	12.6	10.7
Fruits	5.4	5.1	5.5	6.1	6.8	6.1
Dairy products	6.8	6.2	6.2	6.0	6.1	6.3
Fried foods	2.0	1.8	1.9	1.8	1.7	1.7

*Data are percentages unless otherwise indicated.
†Standardized for age to the total cohort.
‡Information ascertained on the 12-month questionnaire.

Table 2.—Relative Risk of Sudden Death According to Dietary Fish Intake*

Servings of Fish Consumed	No. of Cases	Person-Years	Age-Adjusted RR (95% CI)	Multivariate RR (95% CI)†
<1 per mo	9	7715	1.0 (Referent)	1.0 (Referent)
1-3 per mo	12	15 465	0.68 (0.29-1.62)	0.64 (0.26-1.58)
1-<2 per wk	38	79 561	0.42 (0.21-0.88)	0.47 (0.23-0.98)
2-<5 per wk	64	123 693	0.46 (0.23-0.93)	0.51 (0.25-1.04)
≥5 per wk	10	27 343	0.34 (0.14-0.83)	0.39 (0.15-0.96)
P value for trend			.03	.11
<1 per mo	9	7715	1.0 (Referent)	1.0 (Referent)
1-3 per mo	12	15 465	0.68 (0.29-1.62)	0.64 (0.26-1.58)
≥1 per wk	112	230 597	0.44 (0.22-0.86)	0.48 (0.24-0.96)
P value for trend			.006	.03

*RR indicates relative risk; CI, confidence interval.
†The multivariate model includes age (continuous), aspirin and beta carotene treatment assignment, evidence of cardiovascular disease (angina, myocardial infarction, stroke, transient ischemic attack, percutaneous transluminal angioplasty, or coronary artery bypass grafting) prior to 12-month questionnaire, body mass index (quartiles), smoking status (current [<20 cigarettes per day, ≥20 cigarettes per day], past, never), history of diabetes, history of hypertension, history of hypercholesterolemia, alcohol consumption (≤monthly, weekly, daily), vigorous exercise (<weekly, ≥weekly), and vitamin E, vitamin C, and multivitamin use.

dairy, and fried foods) were not significantly associated with sudden cardiac death. The separate addition of these food groups to the multivariate model did not alter the association between fish intake and sudden cardiac death. In analyses according to type of fish, the multivariate RR for men who consumed fish at least once per week as compared with those who consumed less than 1 serving per month was 0.66 (95% CI, 0.40-1.11) for tuna, 0.98 (95% CI, 0.56-1.70) for dark meat fish, 0.63 (95% CI, 0.39-1.04) for other fish, and 0.69 (95% CI, 0.35-1.34) for shellfish. These results are consistent with a possible beneficial effect across various fish categories. For dark meat fish, the point estimate was close to 1.0; however, the CIs for this type of fish were wide and do not exclude the degree of protection seen for other types of fish.

The relationship of estimated intake of n-3 fatty acids with sudden death is shown in Table 3. The mean monthly n-3 fatty acid intake was 5.9 g, which is roughly equivalent to 1 fatty fish meal per week. The reference group rarely or never consumed fish and therefore had a n-3 fatty acid intake from marine sources essentially equal to zero (<0.3 g per month). The remainder who consumed fish were separated into quartiles of n-3 fatty acid intake. There was no significant linear trend across quartiles of n-3 fatty acid intake in either the age-adjusted or the multivariate analyses, but the men who consumed any quantity of n-3 fatty acids had a decreased RR of sudden death (although this reduction was not significant in all quartiles). Spline regression modeling also suggested the existence of a plateau of risk at low intakes, but the CIs were wide (Figure 2).

Other Cardiovascular End Points

There were 737 incident myocardial infarctions during the 11 years of follow-up. In contrast to the inverse relationship with sudden cardiac death, dietary fish consumption and n-3 fatty-acid intake were not associated with myocardial infarction (Table 4). Men who consumed any amount of fish more than once per month had a risk of myocardial infarction equivalent to those who consumed fish less than once per month. Fish consumption also was not significantly associated with nonsudden cardiac death (terminal illness >1 hour) or with risk of coronary heart disease death or total cardiovascular death over either 3 or 5 categories of fish intake (Table 5). However, fish consumption at a level of 1 fish meal per week was associated with a statistically significant reduction in the risk of total mortality after multivariate adjustment (RR for ≥1 meals per week vs <1 meal per month=0.70; 95% CI, 0.55-0.89), with a similar relationship (an apparent threshold at 1-<2 meals
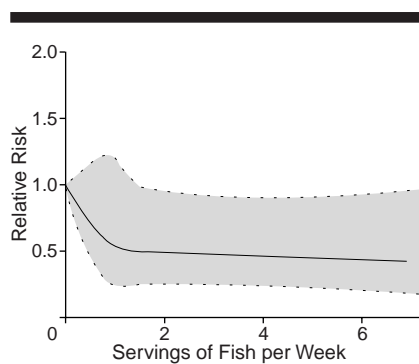

Figure 1.—Multivariate adjusted relative hazard of sudden death across increasing levels of fish intake expressed as servings of fish per week. The solid line represents the maximum partial likelihood estimate of the smooth relative hazard function, using a restricted cubic spline model with 4 knots. The dotted lines represent pointwise 95% confidence intervals for the relative hazard function.
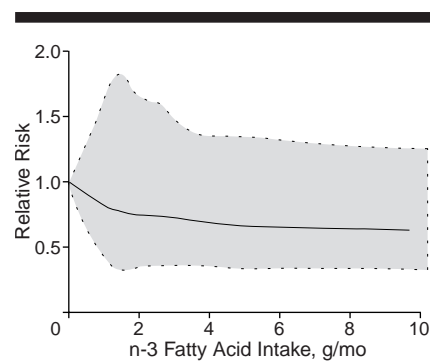

Figure 2.—Multivariate adjusted relative hazard of sudden death across increasing levels of n-3 fatty acid intake from seafood in grams per month. The solid line represents the maximum partial likelihood estimate of the smooth relative hazard function, using a restricted cubic spline model with 5 knots. The dotted lines represent pointwise 95% confidence intervals for the relative hazard function.

Table 3.—Relative Risk of Sudden Death According to Dietary Intake of n-3 Fatty Acid*

Quartile	Range of n-3 Fatty Acid Intake, g/mo	No. of Cases	Person-Years	Age-Adjusted RR (95% CI)	Multivariate RR (95% CI)†
Referent	<0.3	9	7715	1.0 (Referent)	1.0 (Referent)
1	0.3-<2.7	40	65 223	0.55 (0.27-1.14)	0.58 (0.28-1.21)
2	2.7-<4.9	19	56 083	0.30 (0.14-0.67)	0.34 (0.15-0.75)
3	4.9-<7.4	37	61 936	0.53 (0.26-1.10)	0.60 (0.29-1.27)
4	≥7.4	28	62 820	0.40 (0.19-0.85)	0.43 (0.20-0.93)
P value for trend				.13	.21

*RR indicates relative risk; CI, confidence interval.
†See second footnote to Table 2 for description of multivariate model.

per week) to that seen with sudden cardiac death (P for trend across 3 categories=.003; significant after Bonferroni correction, P=.02) (Table 5).

COMMENT

In this large, prospective cohort study of US male physicians, low to moderate intake of fish—at least 1 fish meal per week—was associated with a 52% lower risk of sudden death compared with less than monthly consumption, even after controlling for several confounders. All levels of fish consumption were associated with a decreased risk of sudden death, but the size of the reduction did not appear to differ substantially at levels of consumption greater than 1 fish serving per week, suggesting a threshold effect. This small amount of fish may be sufficient to provide an essential amount of long-chain n-3 polyunsaturated fatty acid or some unidentified nutrient or both that decrease sudden cardiac death. The effect was consistent across most categories except for dark meat fish. If n-3 fatty acids are indeed the active agent, this result is somewhat surprising, because this type of fish has the highest n-3 fatty acid content. However, considering that the CIs were wider for this type of fish and included the degree of protection seen for the other types of fish, a possible benefit for this type of fish cannot be excluded.

When total marine n-3 fatty acid intake was estimated, any intake was associated with a decreased risk of sudden death compared with no intake, but there was no suggestion of a linear dose-response relationship. The lack of a clear dose-response trend and the results for dark meat fish raise the possibility that some other nutrient(s) may play a role in explaining the protective effect of fish consumption on sudden death. Alternatively, if the dose of n-3 fatty acids required for a protective effect was small, these data could be consistent with n-3 fatty acids being the essential nutrient. Also, any significant imprecision in the estimate could have obscured a dose response, especially at the low levels. Our assessment of total n-3 fatty acid intake was subject to both random measurement error and underestimation error owing to a lack of information on α-linolenic acid consumption (an 18-carbon n-3 fatty acid found in unhydrogenated soybean oil, canola oil, and some nuts), which also may have antiarrhythmic properties and can be elongated to eicosapentanoic acid.[26] Both types of errors would tend to reduce or obscure any real association with n-3 fatty acids and may explain the lack of a clear trend.

There was no evidence of any association, in contrast to that seen with sudden cardiac death, between dietary fish (or n-3 fatty acid) intake and the risk of myocar-

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dial infarction. This finding is consistent with previous reports in this[9,27] and other prospective observational studies[10] as well as a secondary prevention trial.[11] The Diet and Reinfarction Trial, which randomized 2033 men after myocardial infarction to receive or not to receive advice to eat at least 2 portions of fatty fish per week, found no difference in the incidence of nonfatal myocardial infarctions between treatment groups at 2 years. Despite this, total mortality (primarily composed of ischemic heart disease deaths) was reduced significantly by 29% in the intervention group. The authors hypothesized that fish consumption may reduce the risk of fatal arrhythmias and therefore mortality after myocardial infarction without affecting the incidence of repeat myocardial infarction. The differential effect on myocardial infarction and sudden death in our prospective study supports this hypothesis, since 91% to 98% of these deaths, as defined, would be expected to be due to a fatal arrhythmia.[28,29]

A component of fish may have antiarrhythmic properties that reduce the vulnerability to life-threatening arrhythmias during cardiac ischemia.[12-14] Consumption of 1 fish meal per week compared with no fish has been associated with an increase in heart rate variability,[30] which has been associated with a lower risk of arrhythmic death after myocardial infarction.[31] There was little added benefit at higher levels of consumption, as seen in our study. A retrospective, population-based case-control study of primary cardiac arrest provides support for antiarrhythmic effects of fish.[15] This study found an association between both dietary intake of n-3 fatty acids from fish and red blood cell n-3 fatty acid composition and a reduced risk of primary cardiac arrest. Also, a decreased risk was seen even at low levels of fish consumption (2 fatty fish meals per month), and a similar reduction was seen at 1 fish meal per week (50% decreased risk). Our study adds to this evidence by demonstrating a similar relationship prospectively between fish and sudden cardiac death in a defined cohort of men.

However, another prospective study found seemingly contradictory results. The Western Electric study[5] reported an association between fish consumption at low doses and a reduced risk of nonsudden but not sudden death from myocardial infarction among 1822 men followed up for 30 years. A major difference between that study and ours was the method used to ascertain the end point of sudden death. The Western Electric study used death certificates alone to determine the specific type of coronary heart disease death and whether deaths from myocardial infarction were sudden. We used next of kin reports, medical records, and autopsy re-

Table 4.—Relative Risk of Myocardial Infarction According to Dietary Fish Intake*

Servings of Fish Consumed	No. of Cases	Person-Years	Age-Adjusted RR (95% CI)	Multivariate RR (95% CI)
<1 per mo	23	7607	1.0 (Referent)	1.0 (Referent)
1-3 per mo	42	15 247	0.94 (0.57-1.56)	0.91 (0.55-1.53)
1-<2 per wk	232	78 056	1.00 (0.65-1.57)	0.99 (0.64-1.54)
2-<5 per wk	363	121 611	1.03 (0.68-1.57)	1.03 (0.67-1.58)
≥5 per wk	77	26 797	1.02 (0.64-1.62)	1.00 (0.62-1.60)
P value for trend			.75	.67

*RR indicates relative risk; CI, confidence interval.
†See second footnote to Table 2 for description of multivariate model.

Table 5.—Relative Risk of Other Types of Cardiovascular and Total Mortality According to Dietary Fish Intake*

Servings of Fish Consumed	Person-Years	Nonsudden Cardiac Death (132 Cases)	Coronary Heart Disease Death (308 Cases)	Cardiovascular Mortality (548 Cases)	Total Mortality (1652 Cases)
<1 per mo	7715	1.0 (Referent)	1.0 (Referent)	1.0 (Referent	1.0 (Referent)
1-3 per mo	15 465	0.65 (0.16-2.61)	1.18 (0.59-2.36)	0.96 (0.57-1.61)	0.79 (0.59-1.06)
1-<2 per wk	78 561	1.19 (0.42-3.35)	0.82 (0.45-1.51)	0.79 (0.51-1.23)	0.71 (0.55-0.91)
2-<5 per wk	123 693	1.32 (0.47-3.66)	0.91 (0.50-1.66)	0.84 (0.54-1.30)	0.70 (0.54-0.89)
≥5 per wk	27 343	1.19 (0.38-3.70)	0.81 (0.41-1.61)	0.81 (0.49-1.33)	0.73 (0.55-0.96)
P value for trend		.33	.49	.50	.045
<1 per mo	7715	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)
1-3 per mo	15 465	0.64 (0.16-2.60)	1.18 (0.58-2.36)	0.96 (0.57-1.61)	0.79 (0.59-1.06)
≥1 per wk	230 597	1.25 (0.46-3.43)	0.87 (0.48-1.56)	0.82 (0.53-1.25)	0.70 (0.55-0.89)
P value for trend		.31	.26	.21	.003

*RR indicates relative risk; CI, confidence interval.
†See second footnote to Table 2 for description of multivariate model.

sults to determine the timing of all cardiac deaths (not just those in which myocardial infarction was listed as the cause of death on a death certificate). The rate of misclassification is high and assessment of timing of death may not be valid when death certificate information is not supplemented with hospital records, autopsy data, or interviews with next of kin.[32,33] Kuller et al[34] found that, even when the probability of sudden death ascertained from information on the death certificate was thought to be high, 50% ultimately were found to be nonsudden deaths when all available information was used.

Our study has several limitations. As with any observational study, the association between fish consumption and sudden cardiac death could, at least in part, be due to residual confounding. Fish consumption may be a marker for a healthier lifestyle. In these data, fish consumers were more likely to exercise regularly and to take antioxidant vitamin supplements. However, fish consumption was not a marker for a lower risk of myocardial infarction, which is also a consequence of a healthier lifestyle. Alternatively, fish consumers may be at higher self-perceived risk for coronary heart disease and are eating fish and practicing other healthy lifestyle behaviors to reduce their higher baseline risk. In support of this possibility, fish consumers were more likely to have a history of hypertension or hypercholesterolemia and a family history of coronary heart disease. The net effect of these interrelationships on risk of sudden death is unclear, but these complex relationships may

account for part or all of the association between fish consumption and sudden cardiac death. In addition, only 637 men reported consuming fish less than once a week, and these men may have other unusual characteristics not accounted for in our multivariate model and that may have influenced their risk for sudden death.

Since we did not collect complete information on diet, our study cannot exclude the possibility that some other dietary factor associated with fish consumption could be responsible for the observed association. But when we controlled for intake of red meat, vegetables, fruits, dairy products, fried foods, saturated fat, and beta carotene from the limited information (40 questions) collected, the relationships between fish and sudden cardiac death were essentially unchanged. None of these food groups was independently associated with sudden cardiac death, and the evidence supporting an antiarrhythmic property of fish is greater. Another important limitation of our study is the single measure of fish consumption and, therefore, the inability to account for changes in intake over time, which also would tend to obscure associations if the effect of fish intake or n-3 fatty acid intake is of short duration.

Despite the beneficial association between fish consumption and sudden cardiac death, our study did not show a significant benefit on total cardiovascular disease mortality (or coronary heart disease mortality) and therefore is discordant with some[1-6] but not all[7-10] prospective cohort studies. In general, fish consumption has been associated with lower

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cardiac mortality in populations characterized by low fish intake in which a substantial proportion rarely or never consumed fish,[1-6] but not in those with high levels of fish intake, in which few individuals rarely or never consumed fish.[7-10] Most studies reporting inverse associations found a benefit at a level of consumption at or around 30 g per day or 1 fish meal per week,[1,5] the same low levels at which fish consumption was associated with a possible antiarrhythmic effect in our study and in the study by Siscovick et al.[15] If there were a threshold effect at 1 fish meal per week, this could explain, at least in part, the apparently discordant result on cardiovascular mortality among observational studies. In our study, only 3.1% of the population rarely or never consumed fish and were therefore at highest risk for sudden death. Accordingly, less than 30% of the coronary heart disease deaths occurred suddenly. Therefore, the observed reduction in cardiovascular mortality associated with fish consumption was only modest (11%) and not significant.

The inverse relationship with total mortality without a significant relationship on cardiovascular mortality suggests that there may be associations between fish consumption and other noncardiac causes of death. The n-3 fatty acids are important components of all cell membranes,[35] have been demonstrated to have anti-inflammatory effects, and may have beneficial effects on ulcerative colitis, rheumatoid arthritis,[35] and asthma.[36] Epidemiologic data[4,37,38] suggest that fish consumption and n-3 fatty acids may have a beneficial effect on certain types of cancers. Also, if fish intake decreased the risk of developing ventricular arrhythmias to a variety of insults such as hypoxia, electrolyte disturbances, and acidosis, then it might influence the risk of dying from diverse causes resulting in an overall benefit on total mortality. Although not clearly explained here, the effect on total mortality is both reassuring and intriguing and clearly warrants further study.

Approximately 250 000 sudden cardiac deaths occur in the United States every year.[39] Of these sudden deaths, 55% have no previous history of heart disease,[40] and most die prior to reaching the hospital. Of persons with cardiac arrest who do reach the hospital, only 30% will be discharged alive.[41] Any substantial reduction in arrhythmic and therefore sudden death will require primary prevention efforts in the general population and not just in those with a history of coronary heart disease. If the observed inverse association between low to moderate levels of fish consumption and a reduced risk of sudden death is causal, the public health impact of such an intervention could be substantial, depending on the percentage of the population in the United States and other countries currently eating fish less than weekly. While large-scale randomized trials are necessary to confirm or refute these findings, our data add to the existing totality of evidence that consuming at least 1 meal of fish per week may substantially reduce the risk of sudden cardiac death.

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