Dietary intake of long-chain n−3 polyunsaturated fatty acids and the risk of primary cardiac arrest[1–3]

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ABSTRACT Whether the dietary intake of long-chain n−3 polyunsaturated fatty acids (PUFAs) from seafood reduces the risk of ischemic heart disease remains a source of controversy, in part because studies have yielded inconsistent findings. Results from experimental studies in animals suggest that recent dietary intake of long-chain n−3 PUFAs, compared with saturated and monounsaturated fats, reduces vulnerability to ventricular fibrillation, a life-threatening cardiac arrhythmia that is a major cause of ischemic heart disease mortality. Until recently, whether a similar effect of long-chain n−3 PUFAs from seafood occurred in humans was unknown. We summarize the findings from a population-based case-control study that showed that the dietary intake of long-chain n−3 PUFAs from seafood, measured both directly with a questionnaire and indirectly with a biomarker, is associated with a reduced risk of primary cardiac arrest in humans. The findings also suggest that *1*) compared with no seafood intake, modest dietary intake of long-chain n−3 PUFAs from seafood (equivalent to 1 fatty fish meal/wk) is associated with a reduction in the risk of primary cardiac arrest; *2*) compared with modest intake, higher intakes of these fatty acids are not associated with a further reduction in such risk; and *3*) the reduced risk of primary cardiac arrest may be mediated, at least in part, by the effect of dietary n−3 PUFA intake on cell membrane fatty acid composition. These findings also may help to explain the apparent inconsistencies in earlier studies of long-chain n−3 PUFA intake and ischemic heart disease. *Am J Clin Nutr* 2000;71(suppl):208S–12S.

KEY WORDS n−3 Fatty acids, diet, risk factors, arrythmia, sudden death, cardiac arrest, ischemic heart disease

INTRODUCTION

Whether the dietary intake of long-chain n−3 polyunsaturated fatty acids (PUFAs) from seafood reduces the risk of ischemic heart disease remains a source of controversy, because studies have yielded inconsistent findings (1–12). The differences among cohorts in the range of dietary intake of long-chain n−3 PUFAs might account for the inconsistent findings: compared with no seafood intake, the modest intake of seafood, ie, 1–2 fatty fish meals/wk, is associated with reduced risk of ischemic heart disease mortality, but there is little evidence that higher intake further reduces risk (13). However, the differences in the ischemic heart disease outcomes examined also might account for the inconsistent findings: there is little evidence that intake of these fatty acids reduces nonfatal ischemic heart disease outcomes such as myocardial infarction and angina pectoris (9–12).

Although coronary atherosclerosis is the major determinant of both ischemic heart disease mortality and nonfatal ischemic heart disease, the acute pathophysiologic mechanisms that lead to various ischemic heart disease outcomes differ. For example, ventricular fibrillation, a cardiac arrhythmia that results in out-of-hospital primary cardiac arrest and a major cause of ischemic heart disease mortality, results in part from an increased myocardial vulnerability to life-threatening arrhythmias (14). Studies in experimental animals suggest that recent dietary intake of long-chain n−3 PUFAs, compared with intake of saturated and monounsaturated fatty acids, reduces myocardial vulnerability to ventricular fibrillation, possibly through an effect on myocardial cell membrane composition (15–20).

In this report, the findings of a population-based case-control study of the dietary intake of long-chain n−3 PUFAs from seafood and the risk of primary cardiac arrest among humans (21) are summarized. Because of the wide range of seafood intake in the community, we examined the dose-response relation between dietary intake of long-chain n−3 PUFAs and the risk of primary cardiac arrest. Because we measured both dietary intake and cell membrane concentrations of long-chain n−3 PUFAs, we also explored whether the relation between dietary intake and the risk of primary cardiac arrest might be mediated through alterations in cell membrane fatty acid composition. The findings of this study may help to explain the inconsistent obser-

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vations from prior cohort studies of dietary intake of long-chain n−3 PUFAs and ischemic heart disease.

METHODS

Briefly, we conducted a population-based case-control study in Seattle and King County, WA. We identified all case subjects with primary cardiac arrest, aged 25–74 y, attended by paramedics during 1988–1994 (n = 334). Control subjects were randomly identified from the same defined population, matched by age (within 7 y) and sex (n = 493). We excluded case and control subjects with prior clinically recognized heart disease or other major life-threatening morbidity and those who had taken fish-oil supplements during the prior year. All subjects were married and were residents of King County; their spouses participated in in-home interviews.

To estimate the dietary intake of long-chain n−3 PUFAs from seafood during the prior month, we developed a quantitative food-frequency questionnaire, the seafood intake scale (SIS). The dietary assessment focused on the prior month because cell membrane composition reflects dietary intake over a period of weeks. The SIS included a list of 25 fish and 10 shellfish available in the Pacific Northwest. For each type of seafood consumed, information was collected on the quantity (usual serving size) and frequency (number of servings) of consumption during the prior month. We estimated the overall intake of eicosapentaenoic acid (EPA; 20:5n−3) and docosahexaenoic acid (DHA; 22:6n−3) from seafood by combining the information from the SIS with information on the average EPA and DHA content of each type of seafood and summing the intake across all types of seafood (22–25).

In substudies, we showed both the validity and the reliability of spouse estimates of dietary long-chain n−3 PUFA intake from seafood. Additionally, on the basis of 8 d of food records collected by control subjects, we showed that the estimates of long-chain n−3 PUFA intake were only weakly related to energy intake and the intake of other nutrients such as saturated fat, protein, carbohydrate, fiber, vitamins, and minerals.

Additionally, we assessed the dietary intake of long-chain n−3 PUFAs from seafood indirectly by using a biomarker, the fatty acid composition of red blood cell membranes. Paramedics obtained blood specimens in the field from a subset of case subjects with primary cardiac arrest after essential emergency medical care had been provided and the patient was either clinically stable or resuscitation had proven ineffective. Data from a preliminary study in 18 primates had suggested that cardiac arrest itself alters long-chain n−3 PUFAs in red blood cell membranes only slightly (21). Blood specimens were obtained from control subjects at the time of the in-person interview. The protocol was approved by the University of Washington Human Subjects Review Committee. Laboratory analyses were conducted to estimate red blood cell membrane combined EPA and DHA, expressed as a percentage of the total cell membrane fatty acids.

We used conditional logistic regression analysis to examine the relation of dietary intake and cell membrane concentrations of long-chain n−3 PUFAs with risk of primary cardiac arrest. To explore the data for a nonlinear dose-response relation, we estimated both the linear and the quadratic terms for dietary intake of long-chain n−3 PUFAs in the logistic model. To determine whether the effect of dietary intake of long-chain n−3 PUFAs might be mediated through alterations in cell membrane fatty acid composition, we also examined the effect of dietary intake on the risk of primary cardiac arrest after adjusting for red blood cell membrane concentrations of long-chain n−3 PUFAs and other clinical characteristics. If dietary intake influences risk through cell membrane fatty acid concentrations, we expected any association between dietary intake and primary cardiac arrest to be reduced or eliminated by the inclusion of the cell membrane fatty acid concentrations in the statistical models.

RESULTS

Both the mean dietary intake and red blood cell membrane concentrations of long-chain n−3 PUFAs were lower in case subjects than in control subjects. Mean (±SD) dietary intakes of combined EPA and DHA were 4.3 ± 6.0 and 5.3 ± 5.6 g/mo for case and control subjects, respectively (P = 0.02). Mean (± SD) red blood cell membrane combined EPA and DHA concentration were 4.3 ± 1.1% and 4.9 ± 1.4% of total fatty acids for case and control subjects, respectively (P = 0.002). There was an inverse relation between the dietary intake of long-chain n−3 PUFAs from seafood and the risk of primary cardiac arrest; however, the addition of the quadratic term for dietary intake of long-chain n−3 PUFAs improved the fit of the logistic model with the linear term alone (P = 0.002), a finding consistent with a nonlinear dose-response relation (**Figure 1**).

Compared with no seafood intake, modest intake of n−3 PUFAs (5.5 g/mo, the equivalent of 1 fatty fish meal/wk, was associated with a 50% reduction in the risk of primary cardiac arrest (odds ratio: 0.5; 95% CI: 0.4, 0.8) after adjustment for age, smoking, family history of myocardial infarction or sudden death, saturated fat intake, hypertension, diabetes, weight, height, physical activity level, and education. Further adjustment for other risk factors, including high blood cholesterol concentrations and alcohol and caffeine intake, altered the findings only slightly. There was little evidence that a higher dietary intake of long-chain n−3 PUFAs was associated with a further reduction in the risk of primary cardiac arrest.

There also was an inverse relation between the combined EPA and DHA concentrations of red blood cell membranes and the risk of primary cardiac arrest (**Figure 2**). The addition of a quadratic term did not improve the fit of the model with the linear term for red blood cell membrane long-chain n−3 PUFA concentration (P = 0.80). Compared with a long-chain n−3 PUFA concentration of 3.3% of total fatty acids (the mean value of the lowest quartile), a red blood cell membrane concentration of 5.0% of total fatty acids (the mean of the third quartile) was associated with a 70% reduction in the risk of primary cardiac arrest (odds ratio: 0.3; 95% CI: 0.2, 0.6), after adjustment for other risk factors.

We also explored whether dietary intake of long-chain n−3 PUFAs might influence the risk of primary cardiac arrest by altering cell membrane fatty acid composition. Among the subset of case and control subjects with blood specimens available, dietary intake of long-chain n−3 PUFAs, assessed directly, was inversely related to risk of primary cardiac arrest, after adjustment for other factors (**Figure 3**). However, after further adjustment for differences in the red blood cell membrane fatty acid concentrations, the dietary intake of long-chain n−3 PUFAs was not associated with the risk of primary cardiac arrest: the odds ratios associated with each quartile of dietary intake assessed directly were close to 1.0.

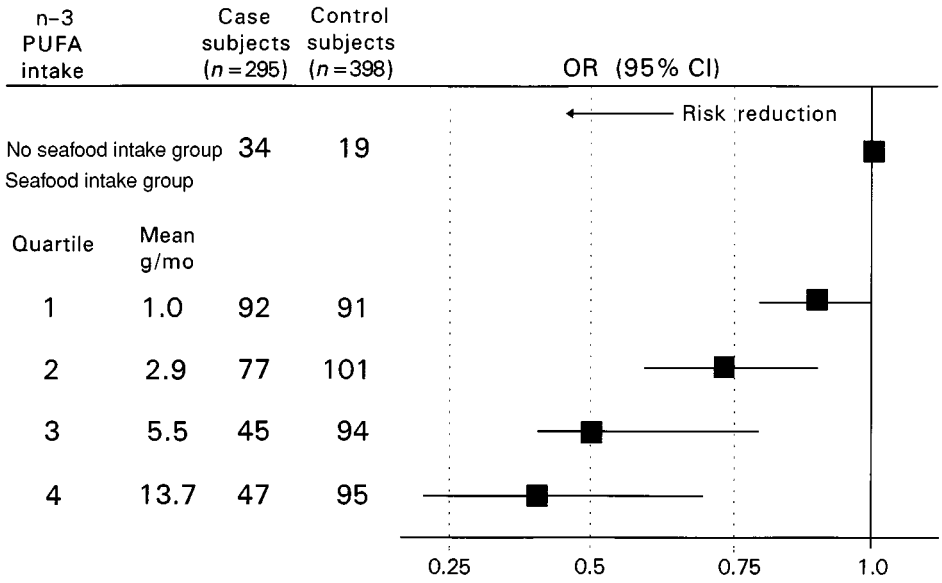

FIGURE 1. Dietary intake of long-chain n−3 polyunsaturated fatty acids (PUFAs) and cardiac arrest. Quartile means are from control subjects. Odds ratios (ORs; ■) and 95% CIs (bars) were from a conditional logistic model that included the linear and quadratic terms for dietary intake of long-chain n−3 PUFAs after adjustment for age, current smoking, former smoking, family history of myocardial infarction or sudden death, fat intake scale (26), hypertension, diabetes mellitus, physical activity level, weight, height, and education. ORs and 95% CIs were calculated by using the no-seafood-intake group as the reference group and the mean value for each seafood intake (long chain n−3 PUFA) category.

DISCUSSION

We assessed the association between the dietary intake of long-chain n−3 PUFAs from seafood and the risk of primary cardiac arrest, an important cause of mortality from ischemic heart disease, in a population with a broad range of dietary intake of long-chain n−3 PUFAs from seafood. Compared with no seafood intake, the consumption of modest amounts of long-chain n−3 PUFAs from seafood [96 g (3 oz) fatty fish/wk, the equivalent of 1 fatty fish meal] was associated with a marked reduction in the risk of primary cardiac arrest. However, there

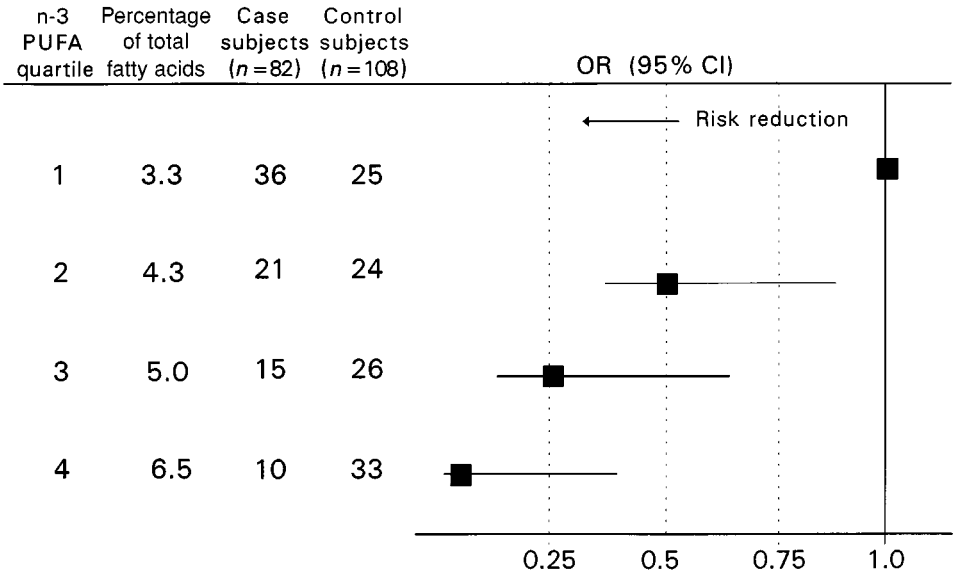

FIGURE 2. Red blood cell membrane long-chain n−3 polyunsaturated fatty acids (PUFAs) and cardiac arrest. Quartile means are from control subjects. Odds ratios (ORs; ■) and 95% CIs (bars) were from a conditional logistic model that included the linear term for red blood cell membrane long-chain n−3 PUFAs after adjustment for age, current smoking, former smoking, family history of myocardial infarction or sudden death, fat intake scale (26), hypertension, diabetes mellitus, physical activity level, weight, height, and education. ORs and 95% CIs were calculated by using the lowest quartile as the reference group and the mean value for each category.

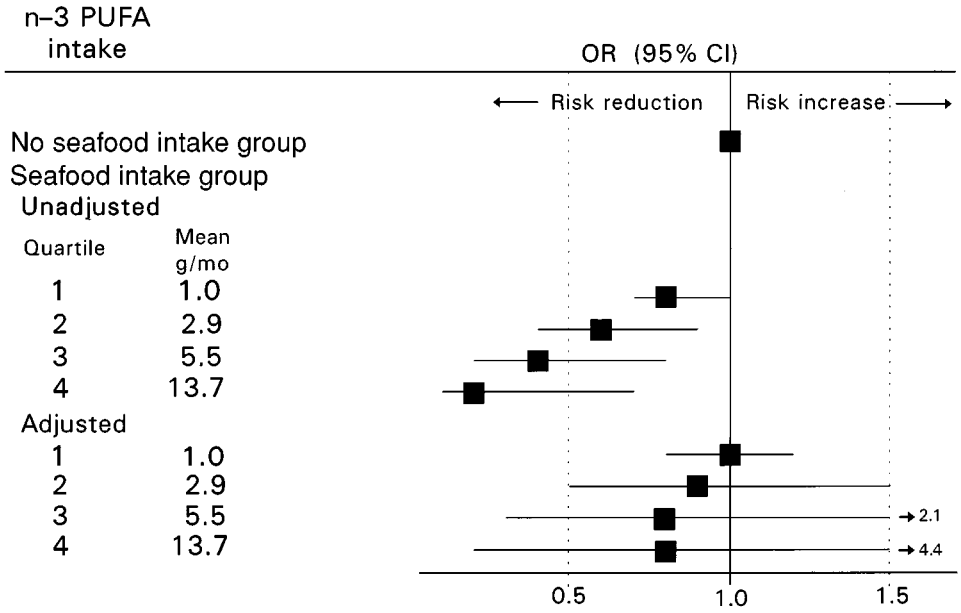

FIGURE 3. Dietary intake of long-chain n−3 polyunsaturated fatty acids (PUFAs) and cardiac arrest with and without adjustment for red blood cell membrane long-chain n−3 PUFAs. Quartile means are from control subjects. Estimates were based on only matched case (n = 82) and control (n = 108) subjects with complete data on red blood cell membrane n−3 fatty acid concentrations and covariates. Odds ratios (ORs; ■) and 95% CIs (bars) are from a conditional logistic model that included the linear and quadratic terms for dietary intake of long-chain n−3 PUFAs, with and without adjustment for red cell membrane long chain n−3 PUFAs, after adjustment for age, current smoking, former smoking, family history of myocardial infarction or sudden death, fat intake scale (26), hypertension, diabetes mellitus, physical activity level, weight, height, and education. ORs and 95% CIs were calculated by using the no-seafood-intake group as the reference group and the mean value of dietary intake for each category.

was little evidence that consumption of higher amounts of long chain n−3 PUFAs was associated with a further reduction in the risk of primary cardiac arrest. Whereas the limitations of an observational study preclude an assessment of potential mechanisms, the findings were consistent with the hypothesis that alterations in cell membrane fatty acid composition may mediate the association between dietary intake of long chain n−3 PUFAs and vulnerability to life-threatening cardiac arrhythmias.

Several limitations of the study need to be considered. We assessed the dietary intake of long-chain n−3 PUFAs by using both a questionnaire and a biomarker: each approach to measurement has limitations. The questionnaire measure relied on the recall of surrogate respondents, ie, the spouses of the subjects. The biomarker measure was influenced also by both intake of other dietary fatty acids and endogenous metabolism of fatty acids. [Of note, the inclusion of docosapentaenoic acid (DPA; 22:5n−3) in the dietary and biomarker estimates of long-chain n−3 PUFA intake from seafood did not alter our findings in a preliminary analysis.] Nevertheless, we suggest that the consistency of the inverse relation between dietary intake of long-chain n−3 PUFAs in 2 different measures that differ in their limitations adds strength to our findings. Also, the results do not preclude bias related to other dietary factors that differ between those who ate seafood and those who did not because we could not obtain a full nutrient assessment from the surrogate respondents. Additionally, the generalizability of our findings to other settings may be limited. The effect of fat intake in the background diet on the observed association is unknown. Furthermore, in other settings, potential adverse effects of toxins found in seafood, eg, mercury, may also alter the benefit-to-risk ratio (12).

Both the magnitude of the risk reduction in primary cardiac arrest and the dose-response relation observed in this study are consistent with the ischemic heart disease mortality risk reduction observed in prior cohort studies (2–12). The findings from this study also are consistent with the findings from 2 secondary prevention trials in patients with a prior myocardial infarction (27, 28). Among men randomly assigned to dietary advice to increase their intake of fish (or n−3 fatty acids from fish oil), there was a 27% reduction in fatal ischemic heart disease but no reduction in the incidence of recurrent nonfatal myocardial infarction (27). In another secondary prevention trial, men randomly assigned to a diet that included a high intake of α-linolenic acid (18:3n−3), the precursor of the long-chain n−3 PUFAs, experienced a significant reduction in total mortality, primarily as a result of a profound reduction in the incidence of cardiac arrest (28). Taken together, these studies suggest that differences in both the range of long-chain n−3 PUFA intake from seafood and the ischemic heart disease outcomes may account for the differences in findings from prior studies.

Studies have also examined the potential mechanisms that underlie these observations (29–31). Studies using isolated myocyte models and voltage clamping have explored the effects of long-chain n−3 PUFAs on the automaticity of isolated cells and the function of sodium, calcium, and potassium channels, respectively. The studies suggest that long-chain n−3 PUFAs may alter electrophysiologic function in a manner that reduces the vulnerability to ventricular fibrillation and that these alterations may explain observations from animal and epidemiologic studies and clinical trials.

For now, public health recommendations to incorporate modest amounts of fatty fish in the diet seem appropriate, given the potential cardiac benefits of modest long-chain n−3 PUFA intake. However, additional primary and secondary prevention trials are needed to evaluate further whether modest dietary intake of long-chain n−3 PUFAs from seafood, low-dose long-chain n−3 PUFA supplements (equivalent in dose to the modest dietary intake from seafood), and intermediate chain n−3 PUFAs, such as α-linolenic acid, reduce ischemic heart disease mortality through a reduction in the incidence of arrhythmic death among persons with low dietary intakes of n−3 PUFAs.

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