n-3 Polyunsaturated Fatty Acids, Fish, and Nonfatal Acute Myocardial Infarction

Alessandra Tavani, SciD; Claudio Pelucchi, SciD; Eva Negri, SciD; Michaela Bertuzzi, SciD; Carlo La Vecchia, MD

Background—The relation between n-3 polyunsaturated fatty acids (PUFAs), fish intake, and risk of coronary heart disease is controversial.

Methods and Results—An Italian case-control study including 507 patients with nonfatal acute myocardial infarction (AMI) and 478 hospital controls found a multivariate odds ratio (OR) of 0.67 (95% CI, 0.47 to 0.95) for the highest n-3 PUFA intake and 0.68 (95% CI, 0.47 to 0.98) for an intake of >1 portion of fish per week compared with ≥2 portions per week.

Conclusions—Small amounts of n-3 PUFAs may be inversely related to AMI risk in this low-risk population. (Circulation. 2001;104:2269-2272.)

Key Words: myocardial infarction ■ epidemiology ■ diet ■ fatty acids ■ risk factors

The hypothesis that consumption of fish and, therefore, of n-3 polyunsaturated fatty acids (PUFAs) reduces the risk of coronary heart disease originated from ecological studies showing that Eskimos had a low incidence of the disease.1 A systematic review of prospective studies found that fish consumption was associated with a reduced risk of coronary heart disease in high-risk populations.2 A study from Finland, Italy, and the Netherlands (part of the Seven Countries Study) showed that fatty fish intake was associated with lower coronary heart disease mortality than was nonfatty fish intake.3 However, in male smokers of the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study cohort, n-3 PUFAs were directly related to coronary death risk,4 and in the National Health and Nutrition Examination Survey (NHANES) I Epidemiologic Follow-up Study, fish intake showed no association with coronary heart disease.5 An Italian case-control study found an odds ratio (OR) of acute myocardial infarction (AMI) of 0.6 for women consuming >1 portion of fish per week.6 An American study7,8 on primary cardiac arrest found an OR of 0.4 for the highest quartile of fatty fish consumption, and a nested case-control study within the Physicians’ Health Study9 found no association between plasma fish oil levels and incidence of AMI. Two clinical trials showed a benefit of fatty fish intake10 or n-3 PUFAs11 on the onset of a second cardiovascular event. Thus, the findings are not consistent, and the strongest associations have been observed in high-risk populations with a low fish intake and in studies with mortality as an end point.12 We evaluated the role of n-3 PUFA and fish intake on nonfatal AMI in a case-control study in Italy, where AMI incidence is low and several dietary correlates are favorable.1

Methods

The data derive from a case-control study of nonfatal AMI, conducted between 1995 and 1999 in the greater Milan, Italy, area. Cases were 507 patients (378 men and 129 women; median age 61 [range, 25 to 79 years]) with a first episode of nonfatal AMI, defined according to the World Health Organization criteria,13 who were admitted to a network of general hospitals in the area. Controls were 478 patients (297 men and 181 women; median age 59 [range, 25 to 79 years]) from the same geographic areas who were admitted to the same hospitals for a wide spectrum of acute conditions unrelated to known or potential AMI risk factors. Among the controls, 34% had traumas; 30%, nontraumatic orthopedic disorders; 14%, acute surgical conditions; and 22%, miscellaneous other illnesses. Fewer than 5% of the cases and controls approached refused interview.

Interviews were conducted in the hospital using a structured questionnaire that included information on socio-demographic factors; anthropometric variables; smoking, alcohol, and other lifestyle habits; a selected medical history; physical activity; and history of AMI in relatives. Information on diet referred to the previous 2 years and was based on a food-frequency questionnaire including 78 foods or food groups.14 Information on fish included weekly frequency of consumption and portion size of 3 items: mixed Mediterranean fish, including clams and mussels (0.94 g of n-3 PUFAs per portion); other fish, including cuttlefish, octopus, and squid (0.49 g of n-3 PUFAs per portion); and canned tuna, mackerel, and sardines (0.34 g of n-3 PUFAs per portion). Content in n-3 PUFAs (including eicosapentaenoic and docosahexaenoic acids) and total energy intake were computed using Italian tables of food composition.15 The correlation coefficient (r) for reproducibility of questions on fish was 0.5916 and that for validity of n-3 PUFAs was 0.64 (derived using data from Decarli et al14).
ORs of AMI and the corresponding 95% CIs for subsequent tertiles of n-3 PUFA and fish intake were derived using unconditional multiple logistic regression, including terms for age, sex, and selected confounding factors (see Tables 1 and 2). Tests for trend were based on the likelihood-ratio test between the models with and without a linear term for each variable of interest.

Results
Compared with patients with the lowest tertile of n-3 PUFA intake, the multivariate OR was 0.67 for those with the highest intake, with a significant trend in risk (Table 1). For fish intake, compared with patients eating fish less than once per week, those eating fish less than twice per week had an OR of 0.79, and those eating fish twice or more per week had an OR of 0.67, with a significant trend in risk. The OR was 0.68 for patients with the highest consumption of fresh fish and 0.70 for those with the highest consumption of canned fish.

The risk of AMI according to tertiles of n-3 PUFAs was not significantly heterogeneous across strata of age, alcohol, hypertension, diabetes (not shown), and sex, although current smokers, patients with higher cholesterol, and those with a family history of AMI in first-degree relatives had an apparently stronger protection (Table 2).

Discussion
Our results indicate that n-3 PUFAs and fish consumption are inversely associated with nonfatal AMI in Italy. In this study, cases and controls were interviewed in the same hospitals and came from the same geographic area, participation was almost complete, and patients admitted for chronic conditions or diseases related to known or potential risk factors for AMI were excluded from controls. There is no reason to assume different recall of fish intake on the basis of the disease status, because the possibility of a relation between fish and AMI was unknown to most subjects. The potential confounding of several covariates, including calorie intake, was allowed for in the analysis. There was no correlation between alcohol intake and fish or n-3 PUFAs (r=0.008 and 0.013, respectively), or between red meat intake and fish or n-3 PUFAs (r=0.013 and -0.041, respectively). Adjustment for meat intake did not modify the OR, suggesting that fish was not a substitute for meat in this population. The food-frequency questionnaire was satisfactorily valid and reproducible. The information on the type of fish consumed was limited. Separate analysis of fresh and canned fish, however, gave similar results.

A potential role for n-3 PUFAs in cardiovascular prevention has been related to their favorable effects on high-density

<table>
<thead>
<tr>
<th>TABLE 1. Distribution of 507 AMI Cases and 478 Controls With Corresponding ORs and 95% CIs, According to n-3 PUFA and Fish Intake</th>
</tr>
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<tbody>
<tr>
<td>AMI Cases</td>
</tr>
<tr>
<td>n-3 PUFAs‡§</td>
</tr>
<tr>
<td>Lowest 199</td>
</tr>
<tr>
<td>Intermediate 139</td>
</tr>
<tr>
<td>Highest 169</td>
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<td>χ², trend</td>
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<tr>
<td>Total fish (portions/wk)‡</td>
</tr>
<tr>
<td>&lt;1 179</td>
</tr>
<tr>
<td>1–&lt;2 178</td>
</tr>
<tr>
<td>≥2 150</td>
</tr>
<tr>
<td>χ², trend</td>
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<tr>
<td>Fresh fish (portions/wk)‡§</td>
</tr>
<tr>
<td>&lt;1 186</td>
</tr>
<tr>
<td>1–&lt;2 203</td>
</tr>
<tr>
<td>≥2 118</td>
</tr>
<tr>
<td>χ², trend</td>
</tr>
<tr>
<td>Canned fish (portions/wk)‡</td>
</tr>
<tr>
<td>0 188</td>
</tr>
<tr>
<td>&gt;0–&lt;1 199</td>
</tr>
<tr>
<td>≥1 120</td>
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<tr>
<td>χ², trend</td>
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</tbody>
</table>

*Estimates from multiple logistic regression models, including terms for age and sex.  
†Estimates from multiple logistic regression models, including terms for age, sex, education, body mass index, cholesterol, smoking, coffee, alcohol, meat, vegetables, fruit, calorie intake, physical activity, hyperlipidemia, diabetes, hypertension, and family history of AMI in first-degree relatives.  
‡Approximate tertile of intake. The upper cutoff points for the first and second tertile of n-3 PUFA intake were 0.81 and 1.29 g/wk.  
§One missing value.  
||Reference category.  
2270 Circulation November 6, 2001
lipoproteins, cholesterol, and lipid oxidation, although it is not clear whether a small amount of fish has any real effect. A role of cardiac arrhythmias has been suggested. The relationship between intake of n-3 PUFAs, fish, and risk of coronary heart disease is controversial. The apparent inconsistencies among different populations may depend partly on differences in methods of assessing fish intake, n-3 PUFAs content of fish types (fatty or lean), coronary heart disease end points, and baseline risk for coronary heart disease.

The apparently stronger (though not statistically significant) inverse association in current smokers and in subjects with high cholesterol or a family history of AMI agrees with overall evidence from prospective studies and suggests stronger protection in high-risk subjects. However, an inverse association with moderate fish consumption was found also in low-risk subjects, suggesting that small amounts of n-3 PUFAs may reduce AMI risk in this low-risk population.

References
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