Fish and Heart Disease: What Is the Real Story?

A new study shows no significant associations between n-3 fatty acids or fish intake and heart disease among men who are initially free of cardiovascular disease. These conclusions may somewhat diminish enthusiasm for fish and fish oil as a panacea against heart disease.

The idea that certain foods will protect against certain diseases has great appeal; one might say it is part of our collective unconscious. Therefore, a study 10 years ago showing that people who ate at least some fish suffered less heart disease than those who did not aroused great interest.[1] The groundbreaking studies of Dyerberg and coworkers had already shown that Eskimos had much lower rates of coronary heart disease than Danes,[2] and the Nobel Prize-winning investigations of Samuelsson, Vane, and colleagues on prostaglandins had provided a rational explanation of how this could work.[3] All this gave fish a healthy image that no doubt stimulated consumption in the United States and also helped to sell innumerable capsules of fish oil.

In light of this, the recent study of Ascherio et al.[4] has come as a bit of a damper. They reported no association between fish intake and coronary heart disease in the Health Professionals Follow-up Study. Where does the evidence stand, and how do these new data fit in?

Fish and other seafoods and oils pressed from them, contain a special class of polyunsaturated fatty acids called ω-3 or *n*-3 ("*n* minus three") fatty acids. While we know that tiny amounts of these are essential for the development of the nervous system in fetuses and infants, the effect of *n*-3 fatty acids on coronary risk is less clear. They strongly reduce serum triglyceride levels, but they do not lower low-density lipoprotein (LDL) cholesterol and may even increase it. They affect prostaglandin synthesis and may inhibit platelet aggregation ex vivo and prolong bleeding time, but the effects are modest compared with aspirin.[5]

Other potential effects of *n*-3s on vascular biology are still under investigation. Large amounts of fish oil sometimes lower blood pressure, and in one clinical trial, fatty fish[6] and perhaps also fish oil[7] did reduce death rates in heart attack survivors. However, eating fish does not grant a population immunity from coronary disease. Rates of myocardial infarction are low in the Japanese and high in East-Finns although both populations enthusiastically eat fish. Shekelle and Stamler[8] reviewed the data on Eskimos who, incidentally, ate seal and whale rather than fish. Although the Eskimos had low rates of coronary disease, there are always risks in comparing populations of widely differing habits. The life-style of the Eskimos was quite unusual, and most of them did not live to a very old age. Efficacy of fish oil against restenosis after angioplasty is still uncertain; some trials have shown promising results, but the success rate in one recent large trial was extremely limited.[9]

All the same, there is persistent evidence from prospective epidemiologic studies that death from heart disease is more unusual among men who eat at least some fish than among men who do not. Such a relation was seen in middle-aged men in Zutphen, the Netherlands,[1] in Chicago Western Electric workers,[10] in the control group of the Multiple Risk Factor Intervention Trial (MRFIT),[11] and in 272 elderly Dutch men and women.[12] However, no relation was seen in populations where fish intake was high.[13,14] The epidemiologic picture is even more puzzling when one realizes that the *n*-3 fatty acids found in fish do not appear to be the sole clue. In Kromhout et al.'s study[1] the fish consumed was mostly of a lean variety, and the amounts of *n*-3 fatty acids they provided were measured in milligrams rather than grams per day.

Between 1986 and 1992 mortality from coronary heart disease in white U.S. men aged 45–74 years decreased by 26%,[15] continuing a trend that was set in in the mid 1960s. Americans appear to be doing something right, but did fish help? The Health Professionals Follow-up Study[4] attempted to answer this question. It is the most recent of three large prospective studies conducted by the Harvard School of Public Health; the other two studies are the Nurses' Health Study and the Physicians' Health Study. Diet is an important focus of all three studies, and data generated from these studies have done much to increase the visibility of nutrition research internationally. An essential tool in these studies is a computer-readable questionnaire, which includes 131 food items. Comparisons with biomarkers and with diet records have shown this questionnaire to be about as valid as traditional, more labor-intensive dietary assessment methods.

Previous accounts of the Health Professionals

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cohort have reported protective effects on coronary risk of vitamin E and alcohol, and little or no effect of iron or coffee intake. Ascherio et al.[4] deal with the effects of *n*-3 fatty acids and fish on heart disease. The authors calculated the intake of fish in 1986 by 44,895 health professionals—most of them dentists—and kept track of their health status for the next 6 years. Surprisingly, intake of *n*-3 fatty acids or fish was not correlated with the risk of coronary disease. The number of participants was much larger than in other studies, and the methodology and data analysis were solid. Measurements of fatty acids in adipose tissue[16] subsequently showed that the questionnaire was reasonably reliable in ranking respondents by *n*-3 fatty acid intake.

The authors have carefully spelled out the limitations of their study.[4] First, two-thirds of the men had greatly increased their intake of fish over the 10 years prior to 1986. Some of those increases could have occurred shortly before the baseline investigation in 1986, because the inverse relation between fish consumption and mortality from coronary heart disease was first reported in 1985.[1] Thus, fish intake data may not reflect long-term habits, and changes in fish intake during follow-up may have also attenuated the association. The authors performed separate analyses in men who reported no change in fish intake and again found no effect. However, it is hard for people to remember what they were eating several years ago. Second, fish intake in these educated men was high and was more comparable with that in Norwegians[13] or Japanese[14] than with intakes of U.S. men who had been studied previously.[10,11] The epidemiologic data suggest that any beneficial effect is already obtained with one or two servings of fish per week, and that more does not further reduce risk.

Previous associations with fish intake have been with coronary mortality, while this study focused on the incidence of nonfatal disease or coronary surgery. From this perspective, there is some agreement between the present and previous reports, because risk of death from coronary heart disease was still about 25% lower in health professionals who ate at least some fish than in men eating no fish at all.[4]

Total incidence of coronary disease plus surgery did not go down with fish intake. However, in some of these men the order of events may have been switched around. They may have turned to fish because they felt that they were at increased risk of a heart attack. Men in the highest 20% of *n*-3 fatty acid intake more frequently reported a family history of coronary disease or a personal history of high cholesterol than did men eating less fish. These high-risk medical professionals also showed a more health-conscious behavior in other ways. In addition to eating fish six times a week they smoked less, were more active, and consumed more vitamins, fiber, chicken, and vegetables and less saturated and *trans* fatty acids, red meat, and high-fat dairy products. Both their awareness regarding coronary disease and their higher baseline risk may have increased their chances of undergoing angioplasty or coronary bypass grafting, and these procedures were counted in with coronary events in the epidemiologic analysis. Ascherio et al.[4] were aware that this trend might obscure the beneficial effects of fish consumption on heart disease rates, and therefore re-evaluated their data after excluding men who knew their cholesterol levels, reported elevated risk factors at baseline, or suffered events during the first 4 years of follow-up. They still observed no lowering of coronary risk with increasing intake of *n*-3 fatty acids or fish. However, there is still a question about how specifically men at increased risk were identified.

Ascherio et al.[4] concluded that increasing fish intake beyond one to two servings per week is unlikely to reduce coronary risk substantially in healthy men free of coronary disease. This is a prudent conclusion that could also be extended to fish oil capsules, which provide *n*-3 fatty acids in much larger amounts than commonly consumed from food. Ascherio et al.[4] found even less evidence for an effect on coronary risk of *n*-3 fatty acids than of fish itself, and the study therefore does not support the blanket use of fish oil capsules.

The Health Professionals study[4] should somewhat diminish enthusiasm for fish and fish oil as a panacea against coronary disease. At present there is no strong evidence that eating large amounts of fish will cause a significant decrease in heart disease risk in healthy men, and data in women are even more scant. However, the epidemiologic evidence that eating no fish at all may be detrimental for your heart is remarkably consistent. Fish oil itself might still have value in preventing a second, lethal cardiac event in people who already have suffered one myocardial infarction. A clinical trial of fatty fish and fish oil in heart disease patients in Britain yielded encouraging results[6,7] and another trial along the same lines would be warranted.

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A Regulatory Pathway of Thermogenesis in Brown Fat Through Retinoic Acid

Thermogenesis in brown adipose tissue is achieved by the enzyme that uncouples the respiratory chain from oxidative phosphorylation. This enzyme is regulated by the sympathetic nervous system and, as recently discovered, by transcriptional regulation through retinoic acid (RA). Thus, RA is involved in heat production and, hence, in the regulation of energy balance.

The role of brown adipose tissue in energy expenditure through thermogenesis, and thereby in possible control of obesity, has recently been the subject of intense research. Brown adipose tissue (BAT), as opposed to white adipose tissue (WAT), is distributed in diffuse deposits throughout the body and is very vascular. BAT is enervated by the sympathetic nervous system and denervation causes atrophy, whereas denervation of WAT causes hypertrophy. BAT responds to norepinephrine on β-1 and β-3 receptors. The large number of mitochondria in BAT contrasts with the small number found in WAT. The most important biochemical difference between the two is in the expression in BAT mitochondria of the uncoupling protein (UCP), which is completely lacking in WAT. This protein, of molecular weight 32 kDa, causes the inner mitochondrial membrane to become permeable to protons, thereby uncoupling the respiratory chain from oxidative phosphorylation. Hence, ATP formation declines and the continuing respiration produces heat.[1]

The gene coding for UCP is completely specific for BAT. It is under transcriptional control in BAT development and in the regulation of heat production. Norepinephrine acts on the β-1 and β-3 adrenergic receptors on the BAT cells to stimulate transcription of the *ucp* gene, mediated by intracellular cAMP. Norepinephrine is the principal inducer of UCP. We do not yet know what turns on *ucp* gene transcription in development and differentiation. There must be an additional factor besides adrenergic stimulation, because the large expression of UCP in late fetal development required to meet thermal stress after birth occurs at a time before the sympathetic nervous system has completely developed. The rodent and human *ucp* genes have been sequenced[2] and shown to have elements responsive to cAMP (i.e., secondary to adrenergic stimulation).

A recent report by Alvarez et al.[3] describes the action of retinoic acid (RA) as a transcriptional activator of the *ucp* gene in the development and differentiation of BAT, independent of the adrenergic system. BAT cells of 3-week-old mice from inter-

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