Fish consumption, cancer, and Alzheimer disease

Dear Sir:

The recent article in the Journal by Fernandez et al (1), pointing out that fish consumption reduces the risk of several types of cancer, is an important work that opens the door to increased prevention of such cancers. Chronic inflammation is one of the risk factors for cancer (2). The results of a recent study suggest that nonsteroidal antiinflammatory drugs may prevent colon cancer by suppressing the expression of hepatocyte growth factor (3).

Cancers for which risk is not reduced by fish consumption are likely not influenced by inflammation. Breast cancer, for example, is related to high concentrations of estrogen and progesterone (2). Prostate cancer is strongly associated with consumption of calcium and the nonfat portion of milk and inversely associated with consumption of tomatoes (4). The hypothesis proposed to explain the link between calcium and prostate cancer is that calcium reduces the amount of circulating vitamin D (5), which has been shown to inhibit prostate cancer cell growth (6).

In addition to cancer, fish consumption has been found to reduce the risk of developing Alzheimer disease (7). The hypothesized mechanism is a reduction in inflammation in the cerebral vascular system. The classic β-amyloid deposits of Alzheimer disease tend to coincide with blood vessels in the brain (8). Thus, the inflammation caused by most fatty acids, which are the highest dietary risk factor for Alzheimer disease (7), can be opposed by the n-3 fatty acids in fish oils. This hypothesis is supported by studies showing that frequent consumption of nonsteroidal antiinflammatory drugs reduces the risk of Alzheimer disease (9). Given that fish tend to bioaccumulate toxins, including heavy metals and pesticides, and that the world’s fish stocks are being depleted rapidly, plant-derived alternatives to fish would be desirable. Although a report by Harris (10) indicates that these plant-derived alternatives are not yet equivalent to fish, it is hoped that research will continue on this important topic.

Thus, our understanding of Alzheimer disease, cancer, and heart disease (1) will benefit from a better understanding of the causes, prevention, and role of inflammation in these chronic diseases.

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REFERENCES

Reply to WB Grant

Dear Sir:

We appreciate Grant’s interest in our recent article on fish consumption and cancer risk (1) as well as his comments on the relation between fish consumption and Alzheimer disease. As Grant pointed out, several but not all cancers considered were inversely related to fish consumption (Figure 1). The findings from the case-control studies conducted between 1983 and 1996 in northern Italy have been reproduced in recent case-control studies of cancers of the oral cavity, pharynx, and colorectum. These recent case-control studies were conducted in several regions of Italy and in the Swiss canton of Vaud and used a method similar to ours with a validated food-frequency questionnaire and questions recalling fish consumption (2). For colorectal cancer, there was an inverse association with fish consumption in both the Italian study (odds ratio [OR] = 0.7 for the highest consumption level (3)) and the Swiss study [OR = 0.9 (4)]. The inverse association was even more apparent for cancers of the oral cavity and pharynx, with an OR of 0.6 in the Italian study (5) and of 0.5 in the Swiss study (6). There is, therefore, consistent evidence that fish...
consumption is a favorable indicator of cancer risk in these European populations.

With reference to the beneficial effect of fish consumption and n−3 fatty acid intakes on the development of Alzheimer disease, scarce epidemiologic information is available to date. Besides the ecologic analysis of Grant (7), a prospective cohort study from the Netherlands (8) showed that fish consumption is inversely related to incident dementia [relative risk (RR) = 0.4] and to Alzheimer disease (RR = 0.3). The results of other studies, however, are contradictory (9). Although some reasonable biological mechanisms have been postulated, analytic epidemiologic studies aimed at addressing the role of fish consumption and other dietary factors (including food groups, nutrients, and micronutrients) would contribute to the investigation of the etiology of Alzheimer disease.

Lactose intolerance—a confusing clinical diagnosis

Dear Sir:

We read with interest the paper published recently by Saltzman et al (1) concerning lactose intolerance. We consider it to be of great significance that >40% of the subjects with self-reported lactose intolerance were, according to Saltzman et al (1), lactose digesters. In Finland, ~17% of the population has hypolactasia (2). The Finnish population is very much aware of lactose intolerance because of media coverage. Because milk and milk products are a large part of the Finnish diet, gastrointestinal problems are easily assumed to be caused by milk. Because many lactose mal digesters tolerate small amounts of lactose in their diet without experiencing any gastrointestinal symptoms (3), the concept of lactose intolerance becomes confusing.

Inspired by the interesting results of Saltzman et al (1), we combined our existing data from 4 different studies (4–7). Over the last few years, 68 subjects (mean age: 35 y; range: 18–65 y; 60 females and 10 males) participated in our blinded crossover study...

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trials set up to investigate the biochemical background of lactose intolerance (4–7). We used the 3 most commonly used lactose tolerance tests in these subjects. The diagnostic variables were as follows: increased blood glucose £ 1.1 mmol/L, increased excretion of breath hydrogen ‡ 20 ppm, and excreted urinary galactose £ 20 mg/3 h. Thirty-one subjects had previously received a diagnosis of lactose intolerance by a health care professional and the remaining 37 subjects were self-diagnosed. Using our gold standard of ‡ 2 of the 3 diagnostic variables being positive after ingestion of 50 g lactose in 250 or 300 mL water after an overnight fast (10 h), we found only half of the 31 subjects with a previous diagnosis of lactose intolerance and 40% of the 37 self-diagnosed subjects to be lactose maldigesters (Figure 1).

Surprisingly, one-third of the 29 subjects diagnosed by us as lactose maldigesters had no clinically significant gastrointestinal symptoms for 3 h after ingesting 50 g lactose. At the same time, one-fourth of the 39 lactose digesters experienced clinically significant gastrointestinal symptoms after ingesting the same amount of lactose. However, the gastrointestinal symptoms differed between the lactose maldigesters and the digesters. Flatulence was the most severe symptom in the maldigesters (<40% of the individual maximum scores) and abdominal bloating was the most severe symptom in the symptomatic digesters (>40% of the individual scores). In both of these groups, the severity of the other symptoms was roughly the same (=20%). Clearly, there is a danger that those lactose digesters who experienced symptoms could receive an incorrect diagnosis of lactose intolerance. Thus, it is essential that the diagnostic tests be conducted carefully.

It is obvious that secondary lactose intolerance due to epithelial damage (secondary hypolactasia) is common. Therefore, the diagnosis of lactose intolerance needs to be made with carefully controlled clinical lactose tolerance tests, preferably more than one. In cases in which values are borderline, a repeat test should be conducted, preferably with use of a different diagnostic method after a period of time. It is hoped that more studies concerning the problems related to the diagnosis of lactose intolerance, like that by Saltzman et al (1), will be carried out.

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Programming not metabolic imprinting

Dear Sir:

The recent review by Waterland and Garza (1) builds usefully on the list of programming (or imprinting) mechanisms that I proposed several years ago (2–4) and that are cited in their article. It is pleasing to see these ideas developed further. We pioneered the experimental approach to testing the influence of early nutrition as a complex environmental programming trigger in humans. This has involved the study of thousands of infants and children over the past 2 decades to whom their early diets have been assigned randomly. In some of the original studies we undertook, subjects have now been followed prospectively into late childhood and early adult life. Such studies (recently summarized in reference 4) provide some of the first experimental, as opposed to observational, data on the sensitivity of humans to nutritional programming. These findings, together with many recent observational studies in the field, certainly justify investment now in the study of the fundamental biological mechanisms involved.

However, there is one point on which I would disagree with the authors—terminology. Originally, I used the term programming in this context in the early 1980s (5), and later defined it in the broader context as the tendency of newborn chicks to follow the first moving object (occasionally a human; 6)—again not an obviously metabolic event. Lorenz in fact used the term imprinting not metabolic imprinting. I agree that imprinting could be substituted for programming, but this would be confusing because the term has now taken on another biological meaning (imprinted genes). In view of this, the term metabolic imprinting should be rejected as being conceptually too narrow, possibly confusing, and not a useful advancement on the term programming, which is well-established in the current scientific literature on the subject.

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Reply to A Lucas

Dear Sir:

We are pleased that Lucas found the list of potential mechanisms of metabolic imprinting in our recent review (1) to represent a useful advance to researchers. However, we do not agree with the suggestion that the term imprinting should be rejected. Our principal objective in proposing a working definition of metabolic imprinting was to narrow the focus of our review to a specific family of putative irreversible biological phenomena. This focus was intended to assist in the development of a reasonably complete yet concise list of potential...
underlying mechanisms. This narrow focus, however, is the primary reason Lucas provides to argue against the terminology we elected to use. As explained in our article, one reason imprinting was chosen rather than programming is the inherently reversible nature explicit in the modern, common scientific use of the latter term, i.e., programs are readily modifiable. Hence, his suggestion that the term metabolic imprinting should be rejected may be evaluated best by considering the phenomena of interest and the underlying mechanisms that explain them. For now, we may simply have to agree to disagree. This likely represents a persistent linguistic gap for which we have other examples of well-known trans-Atlantic differences, e.g., flashlight and torch.

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REFERENCE