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COMMENT & RESPONSE

Let Them Eat Fish

To the Editor Evidence presented by Daenen et al¹ cannot be used to make dietary recommendations for humans regarding intake of fish (oils), sources of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Dietary recommendations can be made only in the context of an adequate understanding of human nutrient requirements, dietary intakes, food composition, and nutrient metabolism. Dietary recommendations are developed by national agencies on the basis of rigid prespecified standards of evaluation of available evidence. There are currently no formal recommendations for fish oil intake as such, but recommendations for intake of ω -3 fatty acids, α -linolenic acid [18:3(n-3)], and EPA+DHA among the healthy population are defined in some countries and regions. Rodent data are not a basis for determining human nutrient requirements or dietary recommendations.

The relevance of 16:4(n-3) (hexadeca-4,7,10,13-tetraenoic acid) to human health is overstated by the authors,¹ who refer to fish oil supplements or plasma as containing “relevant,” “elevated,” and “very high” levels of 16:4(n-3). The highest level of 16:4(n-3) found in any of the fish oil supplements tested is equivalent to 2×10^{-10} percent of the fatty acids found in typical human diets (based on a daily fat consumption of 70 g). A transient increase in 16:4(n-3) level was observed in plasma of healthy study participants following ingestion of fish oil to a maximum level of 400 nM, “20 times the baseline levels” that represents approximately 3.2×10^{-4} percent of total plasma fatty acids. These amounts would not be expected to be of consequence to human health.

High levels of fish intake are typical in certain countries (such as Japan), and no evidence exists for chemotherapy resistance in these countries.

Murphy et al² reported that clinical benefit improved from 36% to 80% in patients with lung cancer who consumed fish oil (providing 2.2 g of EPA per day) throughout platinum-based doublet therapy (6 to 16 weeks). A clinical study providing DHA alone to women with advanced breast cancer reported median overall survival to be extended from 18 to 36 months.³ Several other benefits of fish oil ingestion have been reported during active cancer treatment.^{4,5} The wealth of literature derived from preclinical models supports the clinical studies and suggests that fatty acids found in fish oils improve the therapeutic index of multiple chemotherapies by increasing their efficacy, reducing their toxicity, or both; however, none of this literature was discussed by Daenen et al.¹

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To the Editor Daenen et al “advise patients to temporarily avoid fish oil” and also to “avoid herring and mackerel in the 48 hours surrounding chemotherapy exposure.”^{1(p357)} Dietary recommendations, standards, and regulations are in the purview of regulatory agencies (eg, Food and Drug Administration, Health Canada). These organizations define nutrition-related health policies for the specific nutrients that are essential for the maintenance of growth, development, and health; they also define the upper safe limits of foods, nutrients, and food contaminants (eg, mercury in wild fish). There are high standards of evidence for the evaluation of health claims related to diet and for setting recommendations that form nutrition-related health policy. Regulatory authorities convene expert panels and base their decisions on the entire body of evidence relevant to the question or claim, and the quality and rigor of the methods used to obtain said evidence are critically reviewed.

Search on the terms *fish oil*, *n-3 fatty acids*, and *cancer* brings up several hundred articles. It is not imaginable that the authors of every individual research study would promulgate a nutrition health claim related to their findings. This would serve no end but to strew confusion among patients and clinicians alike as to the potential benefits and risks, if any. A few experimental studies examined the interaction between antineoplastic therapy and n-3 polyunsaturated fatty acids (n-3 PUFAs) derived from the oil of fatty marine fish. The findings show no consistent theme—there are suggestions that certain individual n-3 PUFAs sensitize tumors to chemotherapy and may reverse chemoresistance,^{2,3} as well as others suggesting the opposite.^{1,4} As Daenen et al¹ concede in the Discussion of their article, there are no clinical data to support their advice. It is reassuring that standard chemotherapy has not been noted to lack efficacy in countries such as Japan, Greenland, or Norway, where fatty marine fish is a staple in the diet and typical daily intakes are well in excess of the amounts that Daenen et al¹ claim to induce chemoresistance.

It thus seems premature on the part of Daenen et al¹ to suggest an international change in dietary practices during cancer treatment.

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In Reply Mazurak et al and Baracos provide a welcome discussion on a topic that is subject to debate: fish oil use in anticancer therapy and—in a broader context—the use of supplements by patients with cancer in general. It is becoming increasingly clear that use of certain supplements can impair the effectiveness of chemotherapy and other anticancer therapies. Examples are St John's wort and betacarotene.

There is no discussion on the necessity of ω -3 fatty acids as essential parts of a healthful diet. These fatty acids are not produced by the body and have to be ingested from dietary sources. However, it is important to realize that fish oil is a complex and unstandardized mixture of fatty acids. Its production requires no Food and Drug Administration review or approval. The identity and function of a large part of ω -3 fatty acids present in fish oil remains unclear, and it might therefore contain unknown biologically active molecules. We have identified 16:4(n-3) as an example, which induces chemoresistance in preclinical tumor models.^{1,2} This effect is seen when minor quantities of 16:4(n-3) are administered, which is underscored by the calculations performed by Mazurak et al.

In our article we show that 16:4(n-3) is effectively taken up into the blood of humans after fish oil or fatty fish intake, but the plasma peak is limited to the first hours after intake and depends on the amount ingested.³ We have analyzed epidemiological data sets for information on the type, dose, or timing of fish or fish oil consumption in relation to chemotherapy. Unfortunately, it is not possible to extract this type of information, making it impossible to draw conclusions on 16:4(n-3) exposure and to correctly interpret statements on the effectiveness of chemotherapy in countries with high levels of fish consumption.

Mazurak et al cite a small clinical study to support their arguments, including 15 patients with lung cancer treated with chemotherapy and fish oil. No information was provided on 16:4(n-3) content of the supplement that was used. Larger prospective trials with well-defined fish oil products are not available. On the basis of our preclinical findings, we believe that a trial with 16:4(n-3)-containing fish oil supplements would not be ethical.

In the last few years, meta-analyses on fish oil have shown no benefits of the use of these supplements in prevention of cognitive decline,⁴ or the risk of major cardiovascular events.⁵ Moreover, the use of fish oil was found to be potentially harmful in patients with acute lung injury.⁶ Our preclinical studies now show that many bioactive molecules such as 16:4(n-3) may be present in fish oil supplements, which can adversely affect anticancer treatment. These fatty acids may be circulating in the blood of patients after ingestion of fish oil. In the absence of a US Food and Drug Administration-controlled product and of convincing clinical evidence to support fish oil use during chemotherapy, we believe that physicians and patients should be made aware of these findings, and that caution is required when chemotherapy is combined with fish oil consumption.

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Pricing and Value of Cancer Drugs

To the Editor Mailankody and Prasad¹ identify many important cancer treatments approved by the Food and Drug Administration. However, by failing to account for the complex and variable ways progress occurs, as well as the role