

Effects of Omega-3 Fatty Acids on Cancer

Summary

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Introduction

This report was requested by the Agency for Healthcare Research and Quality (AHRQ), the National Institutes of Health (NIH) Office of Dietary Supplements, and several other NIH institutes. It is one of several reports focusing on the role of omega-3 fatty acids in the prevention or treatment of various diseases. Three Evidence-based Practice Centers (EPCs) produced this series of reports: the Southern California EPC ([SCEPC], based at RAND), the Tufts-New England Medical Center EPC, and the University of Ottawa EPC. This particular report focuses on the effects of omega-3 fatty acids on cancer, specifically tumor incidence, clinical outcomes after cancer treatment, and tumor behavior.

Over the past 40 years, an increasing number of physiological functions have been attributed to omega-3 fatty acids, including movement of calcium and other substances into and out of cells, relaxation and contraction of muscles, and regulation of clotting and secretion of substances that include digestive enzymes and hormones. Omega-3 fatty acids also play a role in the control of fertility, cell division, and growth, suggesting they may protect against certain types of cancer or may alter the response to cancer treatment.^{1,2}

The major dietary sources of omega-3 fatty acids in the U.S. population are fish, fish oil, vegetable oils (principally canola and soybean), walnuts, wheat germ, and some dietary supplements.

Methodology

Study Questions

We convened a technical expert panel composed of distinguished basic scientists and clinicians with established expertise in omega-3 fatty acids, human nutrition, dietary assessment methods, cancer biology, and oncology. The technical expert panel advised us on refining the preliminary questions posed to us by AHRQ, determining the proper inclusion/exclusion criteria for the study and the populations of interest, establishing the proper outcomes measures, and conducting the appropriate analyses.

Based on the original questions received from AHRQ and input from our technical expert panel, we addressed the following questions in this study:

Tumor Incidence:

- What is the evidence that omega-3 fatty acids reduce the incidence of tumors?
- If omega-3 fatty acids influence the incidence of tumors:
 - For what type of tumors?
 - Is there an inverse relationship with intake?
 - Is there a temporal relationship with intake?
 - What is the evidence that genes involved in omega-3 fatty acid transport or metabolism influence the magnitude or direction of the influence on tumor incidence?



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- What is the evidence that the response to omega-3 fatty acids is independent of the intake of antioxidants such as vitamin E or other bioactive food components?
- What is the evidence that the response is modified by the state of the immune system?

Effects on Clinical Outcomes after Cancer Treatment:

- What is the evidence that omega-3 fatty acids alter the effects of cancer treatment on malignant tumors and clinical outcomes after cancer treatments?
- What is the evidence that the response to omega-3 fatty acids is independent of the intake of antioxidants such as vitamin E or other bioactive food components?
- What is the evidence that the response is modified by the state of the immune system?

Tumor Behavior:

- What is the evidence that omega-3 fatty acids alter the behavior of malignant tumors in terms of growth, differentiation, and apoptosis?
- If omega-3 fatty acids influence the behavior of tumors:
 - For what type of tumors?
 - Is there an inverse relationship with intake?
 - Is there a temporal relationship with intake?
 - What is the evidence that genes involved in omega-3 fatty acid transport or metabolism influence the magnitude or direction of the influence on tumor behavior?

Search Strategy

Jessie McGowan, Senior Information Scientist, and Nancy Santesso, Knowledge Translation Specialist, at the University of Ottawa were responsible for developing a common search strategy for omega-3 fatty acids for the three participating EPCs. Nancy Santesso developed a core omega-3 search strategy in collaboration with project librarians, biochemists, nutritionists, and clinicians, who also provided biochemical names, abbreviations, food sources, and commercial product names for omega-3 fatty acids. The literature search was not restricted by language of publication or by study design, in order to increase sensitivity. When possible, the searches were limited to studies involving human subjects. For the SCEPC, this core search strategy was incorporated into a specific search for cancer.

In consultation with our technical expert panel and the task order officer, it was decided that, for the questions pertaining to tumor behavior, i.e., apoptosis, tumor growth, and differentiation, we would conduct a separate search focusing on review articles and meta-analyses of animal studies and cell culture studies pertaining to both humans and animals.

The following databases were searched: MEDLINE® (1966-October week 5, 2003), PreMEDLINE® (Nov 7, 2003), EMBASE (1980-Week 44, 2003), Cochrane Central Register of Controlled Trials (3rd Quarter, 2003), CAB HEALTH® (1973-October 2003). All of these databases were searched using the OVID interface, except CAB HEALTH, which was searched through SilverPlatter. Any duplicate records were identified and removed within each search question using Reference Manager® software. The citations obtained from these literature searches were sent to the SCEPC via e-mail. In addition, we sent letters to industry experts recommended by the Office of Dietary Supplements to obtain any unpublished data.

Selection Criteria

Two reviewers independently reviewed each article considered for inclusion in the study. Any disagreements between the reviewers were resolved through consensus. For the questions pertaining to tumor incidence and response to treatment, we included any articles that pertained to the effects of omega-3 fatty acids on cancer, presented research on human subjects, and reported the results of randomized clinical trials, controlled clinical trials, or cohort/case control studies. We were unable to identify human studies that assessed the effects of omega-3 fatty acids on tumor behavior, i.e., cell growth, differentiation, and apoptosis. Hence, to evaluate the effects of omega-3 fatty acids on tumor behavior, we turned to the animal and cell culture literature. The initial intent was to summarize only meta-analyses and systematic reviews; however, because a total of only one meta-analysis and four systematic reviews were identified, the decision was made to summarize all relevant reviews. Language was not a barrier to inclusion.

Data Extraction and Analysis

For each article on tumor incidence and response to treatment included in the study, two reviewers independently extracted data about the trial design; the outcomes of interest; the quality of the trial; the number and characteristics of the patients; details on the intervention, such as the dose, frequency, and duration; the types of outcome measures; adverse events; and the elapsed time between the intervention and outcome measurements. Any disagreements between the reviewers were resolved through consensus. For each article, we then evaluated the quality of the design and execution of trials using a system developed by Jadad;³ determined a combined applicability grade based on applicability to the U.S. population and health state; performed a meta-analysis of those studies that sufficiently assessed interventions, populations, and outcomes to justify pooling; and performed a qualitative analysis of the remaining studies. The reviews and meta-

analyses on tumor behavior were reviewed and summarized by the medical editor, a nutritional biochemist.

Findings

Tumor Incidence and Outcomes after Cancer Treatment

We screened 4,834 article titles. From these article titles, we chose to review 1,210 full-text articles. Of these full-text articles, 356 met our selection criteria and were chosen for data extraction. After data extraction, 52 articles met our inclusion criteria: 33 reported on cancer incidence, and 19 reported on cancer treatment (all 19 reported on surgery). The 19 cohorts that participated in the studies of tumor incidence varied widely with respect to demographics and intake of omega-3 fatty acids.

Omega-3 Fatty Acids and Tumor Incidence

Among 43 risk ratios calculated across the 19 cohorts for 11 different types of cancer and 5 different ways to assess omega-3 fatty acid consumption (fish consumption, total omega-3 consumption, alpha-linolenic acid [ALA] consumption, docosahexaenoic acid [DHA] consumption, and eicosapentaenoic acid [EPA] consumption), only four are statistically significant. Significant associations between omega-3 consumption and cancer risk were reported for lung cancer in two studies; for breast cancer in one; for prostate cancer in one; and for skin cancer in one. However, for lung cancer, one of the significant associations was for increased cancer risk and the other was for decreased risk (four other risk ratios were not significant for lung cancer). For breast cancer, five other estimates did not show a significant association. Only one study assessed skin cancer risk. No effects were reported for cancers of the aerodigestive tract, bladder cancer, colorectal cancer, lymphoma, ovarian cancer, pancreatic cancer, or stomach cancer. Thus, omega-3 fatty acids do not appear to decrease overall cancer risk.

Temporal and/or Dose-Response Relationship between Tumor Incidence and Omega-3 Fatty Acid Intake

Data were insufficient to permit assessment of a temporal or dose-response relationship.

Evidence for Involvement of Genes for Omega-3 Fatty Acid Transport or Metabolism

No studies were identified that investigated the role of omega-3 fatty acid transport or metabolism genes in any putative effect of omega-3 fatty acids on tumor incidence.

Evidence for Dependence on Intake of Antioxidants or Other Bioactive Food Components

No studies were identified that allowed this question to be answered.

Evidence for Modification of Response to Omega-3 Fatty Acids by Immune Status

No studies were identified that examined the possible modification of the effect of omega-3 fatty acids by immune status.

Effect of Omega-3 Fatty Acids on Clinical Outcomes

We identified 19 studies from which the effect of omega-3 fatty acids on clinical outcomes after cancer therapy could be ascertained, all of which pertained to patients who had undergone cancer surgery for upper gastrointestinal malignancies. We did not identify any studies that assessed the effects of omega-3 fatty acids on clinical outcomes after chemotherapy or radiation surgery. Among the identified studies, 14 described the effect on post-operative complications, 13 on hospital length of stay, 10 on mortality, 11 on nutrition and three on weight. In pooled analyses, omega-3 fatty acids had no effect compared to placebo on post-operative complications, hospital length of stay, or mortality. With the exception of one study that demonstrated higher mean nitrogen intake for subjects treated with omega-3 fatty acids relative to placebo, no significant effect on nutrition or weight loss was observed.

Evidence for Dependence of Effects on Clinical Outcomes on Intake of Antioxidants or Other Bioactive Food Components

No studies were identified that allowed this question to be answered.

Evidence for Modification of Effects on Clinical Outcomes by Immune Status

No studies were identified that examined the possible modification of the effect of omega-3 fatty acids on clinical outcomes by immune status.

Tumor Behavior

To assess the effects of omega-3 fatty acids on tumor growth, differentiation, and apoptosis in animal and in vitro models, we screened a total of 369 citations, of which 82 were considered relevant. Of those 82, 60 could be retrieved. Of the 60, 27 were accepted for further review because they reviewed the effects of omega-3 fatty acids (added to the diet or to cell

cultures) on cancer development, apoptosis, or cell differentiation in laboratory animals or cell culture systems.

Although much of the evidence favored a role for dietary omega-3 fatty acid enrichment in the inhibition or prevention of colon, mammary, pancreatic, and prostate tumor growth, at least in some animal models, the quality of the reviews is not sufficient to permit strong conclusions to be drawn.

Evidence was presented in a small number of reviews that omega-3 fatty acids can stimulate cellular differentiation and apoptosis, two proposed mechanisms for the inhibition of tumor development and proliferation; however, the evidence is insufficient to assess the relevance of these findings.

Evidence for an Inverse or Temporal Relationship with Intake

Insufficient evidence was presented to assess dose-response effects or to ascertain the stage of tumor development that might be affected by omega-3 fatty acids.

Evidence that Genes Involved in Omega-3 Fatty Acid Transport or Metabolism Influence the Magnitude or Direction of the Influence on Tumor Behavior

Several reviews provided evidence that omega-3 fatty acids may affect tumor behavior by competing with omega-6 fatty acids for the enzymes that metabolize them to their bioactive products or by influencing the genes for these enzymes; however, other evidence suggests an effect on intracellular redox state and the integrity of membrane lipids.

Future Research

Following are our observations and recommendations regarding future research on the effects of omega-3 fatty acids on cancer. Given the large body of evidence that suggests no association between omega-3 fatty acid consumption and cancer incidence, future research in this general area is unlikely to reveal significant associations. However, should new evidence suggest a role for omega-3 fatty acids in the growth or development of a particular type of cancer, studies to assess the effect of omega-3 fatty acids on the incidence of that particular type of cancer might be warranted.

Although existing studies do not demonstrate an effect of omega-3 fatty acids on mortality, hospital length of stay, post-operative complications, or nutrition after cancer surgery, the body of literature is small and does not support strong conclusions. Given a plausible model for an omega-3 effect on outcomes after cancer therapy, future directed trials might be warranted.

Although the body of literature that describes the effects of omega-3 fatty acids on tumor behavior in animal and cell culture models is large, it is heterogeneous in terms of the models used, the carcinogens used and the dose, timing and duration of exposure to omega-3 fatty acids. The development and dissemination of a consensus statement about goals and standards of research in this area might lead to more efficient and fruitful research in this area.

Availability of the Full Report

The full evidence report from which this summary was taken was prepared for the Agency for Healthcare Research and Quality (AHRQ) by the Southern California Evidence-based Practice Center under Contract No. 290-02-0003. It is expected to be available in February 2005. At that time, printed copies may be obtained free of charge from the AHRQ Publications Clearinghouse by calling 800-358-9295. Requesters should ask for Evidence Report/Technology Assessment No. 113, *Effects of Omega-3 Fatty Acids on Cancer*. In addition, Internet users will be able to access the report and this summary online through AHRQ's Web site at www.ahrq.gov.

Suggested Citation

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