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Number 113

Effects of Omega-3 Fatty Acids on Cancer

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-Based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. This report on Effects of Omega-3 Fatty Acids on Cancer was requested and funded by AHRQ. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality improvement projects throughout the Nation. The reports undergo peer review prior to their release.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

We welcome comments on this evidence report. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to **epc@ahrq.gov.**

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Chapter 1 was written in collaboration with the New England Medical Center Evidence-based Practice Center.

Structured Abstract

Context: Clinical trials and observational studies report differing effects of omega-3 fatty acids on cancer.

Objectives: To assess the effect of omega-3 fatty acids on 1) tumor incidence 2) clinical outcomes after cancer treatment, and 3) tumor behavior.

Data Sources: We searched computerized databases to identify potentially relevant studies and contacted industry experts for unpublished data.

Study Selection:

Tumor incidence and outcomes after cancer treatment. We screened 4,834 titles, reviewed 356 articles, and included 52 articles in our review. For tumor incidence, we restricted to prospective cohort studies in humans, and for clinical outcomes after cancer treatment, we restricted to randomized controlled trials (RCTs); We had no language restrictions.

Tumor behavior. We screened 366 titles, reviewed 82 articles, and included 27 articles in our review. For tumor behavior, we restricted to review articles and meta-analyses of animal studies and cell culture studies in humans and animals. We had no language restrictions.

Data Extraction: We abstracted data on study design, study population, and outcomes; source, amount, and duration of omega-3 fatty acid consumption; and randomization, dropouts, blinding, and allocation for RCTs.

Data Synthesis:

Tumor incidence. Across 19 cohorts for 11 different types of cancer and using up to 5 different ways to categorize omega-3 fatty acid consumption, 44 estimates of the association between omega-3 fatty acid consumption were reported. Among these, only six were statistically significant. Significant associations between omega-3 consumption (in the form of both fish and alpha-linolenic acid) and cancer risk were reported for breast cancer in two studies; for lung cancer in two; for prostate cancer in one; and for skin cancer in one. For breast cancer one significant estimate was for increased risk and one was for decreased risk; five other estimates did not show a significant association. For lung cancer one of the significant associations was for increased cancer risk, the other was for decreased risk and four other estimates were not significant. Only one study assessed skin cancer risk.

Cancer treatment. 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 treatment. Among the identified studies, the effect of omega-3 fatty acids alone could be ascertained from six studies; the effect of omega-3 fatty acids given in combination with arginine and RNA could be ascertained from 13. Effects on post-operative complications were described in 14, on hospital length of stay in 13, on mortality in ten, on nutritional parameters in 11, and on weight in three. In pooled analyses, omega-3 fatty acids had no effect compared to placebo on post-operative complications, hospital length of stay, nutritional parameters, or mortality.

Relative to a standard enteral diet, omega-3 fatty acids in combination with arginine and RNA were associated with a reduced risk of postoperative complications (RR 0.51, 95%CI 0.40, 0.64) and reduced length of hospital stay (pooled mean difference -3.33 days, 95%CI -4.29, -2.38). Among nine studies that assessed the effect on nutritional parameters omega-3 plus arginine and RNA, prealbumin was significantly higher in the omega-3 + arginine + RNA group in three studies, but not different in three others; mean nitrogen intake was significantly higher in one study but not in another. No significant differences were found for mean caloric intake, mean albumin, or mean transferrin.

Although the combination of omega-3 fatty acids, arginine, and RNA are associated with a reduced risk of post-operative complications and reduced length of hospital stay, it is not possible to ascertain whether these effects are due to omega-3 fatty acids, arginine, RNA, or a combination of these.

Tumor behavior. We evaluated 27 reviews of studies on animals or cell culture models that described the effects of tumor growth, differentiation or apoptosis. Although much of the evidence favored a role for n-3 dietary enrichment in the inhibition or prevention of tumor growth, at least in some animal models, the quality of the reviews is not sufficient to permit strong conclusions to be drawn.

Conclusions: In a large body of literature spanning numerous cohorts from many countries and with different demographic characteristics, the evidence does not suggest a significant association between omega-3 fatty acids and cancer incidence. In a small body of literature, there is no significant association between omega-3 fatty acids and clinical outcomes after tumor surgery. Although the combination of omega-3 fatty acids, arginine, and RNA are associated with a reduced risk of post-operative complications and reduced length of hospital stay, it is not possible to ascertain whether these effects are due to omega-3 fatty acids, arginine, RNA, or a combination of these. Although a large, but heterogeneous, body of literature suggests that omega-3 dietary enrichment may play a favorable role in the inhibition or prevention of tumor growth in some animal models, the quality of the reviews is not sufficient to permit strong conclusions to be drawn.

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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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Evidence-Based Practice

- 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.

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Evidence Report

Chapter 1. Introduction

This report is one of a group of evidence reports prepared by three Agency for Healthcare Research and Quality (AHRQ)-funded Evidence-Based Practice Centers (EPCs) on the role of omega-3 fatty acids (both from food sources and from dietary supplements) in the prevention or treatment of a variety of diseases. These reports were requested by the National Institutes of Health Office of Dietary Supplements and several institutes at the National Institutes of Health (NIH). The three EPCs – the Southern California EPC (SCEPC, based at RAND), the Tufts-New England Medical Center (NEMC) EPC, and the University of Ottawa EPC – have each produced evidence reports. To ensure consistency of approach, the three EPCs collaborated on selected methodological elements, including literature search strategies, rating of evidence, and data table design.

The aim of these reports is to summarize the current evidence on the effects of omega-3 fatty acids on prevention and treatment of cardiovascular diseases, cancer, child and maternal health, eye health, gastrointestinal/renal diseases, asthma, immune-mediated diseases, tissue/organ transplantation, mental health, and neurological diseases and conditions. In addition to informing the research community and the public on the effects of omega-3 fatty acids on various health conditions, it is anticipated that the findings of the reports will also be used to help define the agenda for future research.

This report focuses on the effects of omega-3 fatty acids on cancer. Other reports from the SCEPC focus on neurological diseases, cognitive function, immune-mediated diseases, bone metabolism, and gastrointestinal/renal diseases.

This chapter provides a brief review of the current state of knowledge about the metabolism, physiological functions, and sources of omega-3 fatty acids.

The Recognition of Essential Fatty Acids

Dietary fat has long been recognized as an important source of energy for mammals, but in the late 1920s, researchers demonstrated the dietary requirement for particular fatty acids, which came to be called essential fatty acids. It was not until the advent of intravenous feeding, however, that the importance of essential fatty acids was widely accepted: Clinical signs of essential fatty acid deficiency are generally observed only in patients on total parenteral nutrition who received mixtures devoid of essential fatty acids or in those with malabsorption syndromes. These signs include dermatitis and changes in visual and neurological function. Over the past 40 years, an increasing number of physiological functions, such as immunomodulation, have been attributed to the essential fatty acids and their metabolites, and this area of research remains quite active.[1, 2]

Fatty Acid Nomenclature

The fat found in foods consists largely of a heterogeneous mixture of triacylglycerols (triglycerides)--glycerol molecules that are each combined with three fatty acids. The fatty acids can be divided into two categories, based on chemical properties: saturated fatty acids, which are usually solid at room temperature, and unsaturated fatty acids, which are liquid at room temperature. The term "saturation" refers to a chemical structure in which each carbon atom in the fatty acyl chain is bound to (saturated with) four other atoms, these carbons are linked by single bonds, and no other atoms or molecules can attach; unsaturated fatty acids contain at least one pair of carbon atoms linked by a double bond, which allows the attachment of additional atoms to those carbons (resulting in saturation). Despite their differences in structure, all fats contain approximately the same amount of energy (37 kilojoules/gram, or 9 kilocalories/gram).

The class of unsaturated fatty acids can be further divided into monounsaturated and polyunsaturated fatty acids. Monounsaturated fatty acids (the primary constituents of olive and canola oils) contain only one double bond. Polyunsaturated fatty acids (PUFAs) (the primary constituents of corn, sunflower, flax seed, and many other vegetable oils) contain more than one double bond. Fatty acids are often referred to using the number of carbon atoms in the acyl chain, followed by a colon, followed by the number of double bonds in the chain (e.g., 18:1 refers to the 18-carbon monounsaturated fatty acid, oleic acid; 18:3 refers to any 18-carbon PUFA with three double bonds).

PUFAs are further categorized on the basis of the location of their double bonds. An omega or n notation indicates the number of carbon atoms from the methyl end of the acyl chain to the first double bond. Thus, for example, in the omega-3 (n-3) family of PUFAs, the first double bond is 3 carbons from the methyl end of the molecule. The trivial names, chemical names and abbreviations for the omega-3 fatty acids are detailed in Table 1.1.

Finally, PUFAs can be categorized according to their chain length. The shorter-chain 18-carbon n-3 and n-6 PUFAs are precursors to the longer 20- and 22-carbon PUFAs, called very-long-chain PUFAs (VLCPUFAs).

Table 1.1. Nomenclature of omega-3 fatty acids.

Names		Abbreviations		
Trivial	IUPAC*	Carboxyl-reference	Omega-reference	Other
Linolenic acid	9,12,15-octadecenoic acid alpha-linolenic acid	$18:3\Delta^{9\ 12\ 15}$	18:3n-3 18:3 (ω-3)	ALA α-LA LNA α-LNA
Docosahexaenoic acid	4,8,12,15,19- docosahexaenoic acid cervonic acid	$22:6\Delta^{4\ 8\ 12\ 15\ 19}$	22:6n-3 22:6 (ω-3)	DHA
Docosapentaenoic acid	7,10,13,16,19-docosapentaenoic acid	$22:5\Delta^{7\ 10\ 13\ 16\ 19}$	22:5n-3 22:5 (ω-3)	DPA
Eicosapentaenoic acid Icosapentaenoic acid Timnodonic acid	5,8,11,14,17- eicosapentaenoic acid	$20:5\Delta^{5\ 8\ 11\ 14\ 17}$	20:5n-3 20:5 (ω-3)	EPA

*IUPAC=International Union of Pure and Applied Chemistry.

Fatty Acid Metabolism

Mammalian cells can introduce double bonds into all positions on the fatty acid chain except the n-3 and n-6 position. Thus, the shorter-chain alpha-linolenic acid (ALA, chemical abbreviation: 18:3n-3) and linoleic acid (LA, chemical abbreviation: 18:2n-6) are essential fatty acids. No other fatty acids found in food are considered 'essential' for humans, because they can all be synthesized from the shorter chain fatty acids.

Following ingestion, ALA and LA can be converted in the liver to the long chain, more-unsaturated n-3 and n-6 VLCPUFAs by a complex set of synthetic pathways that share several enzymes (Figure 1.1). VLC PUFAs retain the original sites of desaturation (including n-3 or n-6).

The omega-6 fatty acid LA is converted to gamma-linolenic acid (GLA, 18:3n-6), an omega-6 fatty acid that is a positional isomer of ALA. GLA, in turn, can be converted to the longer-chain omega-6 fatty acid, arachidonic acid (AA, 20:4n-6). AA is the precursor for certain classes of an important family of hormone-like substances called the eicosanoids (see below).

The omega-3 fatty acid ALA (18:3n-3) can be converted to the long-chain omega-3 fatty acid, eicosapentaenoic acid (EPA; 20:5n-3). EPA can be elongated to docosapentaenoic acid (DPA 22:5n-3), which is further elongated, desaturated, and beta-oxidized to produce docosahexaenoic acid (DHA; 22:6n-3). EPA and DHA are also precursors of several classes of eicosanoids and docosanoids, respectively, are known to play several other critical roles, some of which are discussed further below.

The conversion from parent fatty acids into the VLC PUFAs ─ EPA, DHA, and AA ─ appears to occur slowly in humans. In addition, the regulation of conversion is not well understood, although it is known that ALA and LA compete for entry into the metabolic pathways.

Physiological Functions of EPA and AA

As stated earlier, fatty acids play a variety of physiological roles. The specific biological functions of a fatty acid are determined by the number and position of double bonds and the length of the acyl chain.

Both EPA (20:5n-3) and AA (20:4n-6) are precursors for the formation of a family of hormone-like agents called eicosanoids. Eicosanoids are rudimentary hormones or regulatory-molecules that appear to occur in most forms of life. However, unlike endocrine hormones, which travel in the blood stream to exert their effects at distant sites, the eicosanoids are autocrine or paracrine factors, which exert their effects locally – in the cells that synthesize them or adjacent cells. Processes affected include the movement of calcium and other substances into and out of cells, relaxation and contraction of muscles, inhibition and promotion of clotting, regulation of secretions including digestive juices and hormones, and control of fertility, cell division, and growth.[1]

The eicosanoid family includes subgroups of substances known as prostaglandins, leukotrienes, and thromboxanes, among others. As shown in Figure 1.1, the long-chain omega-6 fatty acid, AA (20:4n-6), is the precursor of a group of eicosanoids that include series-2

prostaglandins and series-4 leukotrienes. The omega-3 fatty acid, EPA (20:5n-3), is the precursor to a group of eicosanoids that includes series-3 prostaglandins and series-5 leukotrienes. The AA-derived series-2 prostaglandins and series-4 leukotrienes are often synthesized in response to some emergency such as injury or stress, whereas the EPA-derived series-3 prostaglandins and series-5 leukotrienes appear to modulate the effects of the series-2 prostaglandins and series-4 leukotrienes (usually on the same target cells). More specifically, the series-3 prostaglandins are formed at a slower rate and work to attenuate the effects of excessive levels of series-2 prostaglandins. Thus, it has been suggested that adequate production of the series-3 prostaglandins could protect against heart attack and stroke as well as certain inflammatory diseases like arthritis, lupus, and asthma.[3]

EPA (20:5 n-3) also affects lipoprotein metabolism and decreases the production of substances – including cytokines, interleukin 1β (IL-1β), and tumor necrosis factor α (TNF-α) – that have pro-inflammatory effects (such as stimulation of collagenase synthesis and the expression of adhesion molecules necessary for leukocyte extravasation [movement from the circulatory system into tissues]).[1] DPA (22:5n-3), the elongation product of EPA, is metabolized to DHA (22:6n-3). DHA (22:6n-3) is the precursor to a newly-described metabolite called 10,17S-docosatriene,[4] which is part of a family of compounds called 'resolvins.'[5] They are synthesized in the brain in response to an ischemic insult and counteract the pro-inflammatory actions of infiltrating leukocytes by blocking interleukin 1-beta-induced NF-kappaB activation and cyclooxygenase-2 expression.[6] DHA also plays a role in retinal rod outer segments by influencing membrane fluidity so as to optimize G protein coupled signaling.[7] The mechanism responsible for the suppression of cytokine production by omega-3 LC PUFAs and VLCPUFAs remains unkown, although suppression of omega-6-derived eicosanoid production by omega-3 fatty acids may be involved, because the omega-3 and omega-6 fatty acids compete for common enzymes in the fatty acid metabolic pathway, including delta-6 desaturase, as well as the rate-limiting enzymes in the eicosanoid pathway – phospholipases A2, cyclooxygenase, and lipoxygenase.

Along with AA, DHA is the major PUFA found in the brain and is thought to be important for brain development and function. Recent research has focused on this role and the effect of supplementing infant formula with DHA (since DHA is naturally present in human breast milk but not in formula).

Dietary Sources and Requirements

Both ALA and LA are present in a variety of foods. LA is present in high concentrations in many commonly used oils, including safflower, sunflower, soy, and corn oil. ALA is present in some commonly used oils, including canola and soybean oil, and in some leafy green vegetables.

Thus, the major dietary sources of ALA and LA are PUFA-rich vegetable oils. The proportion of LA to ALA as well as the proportion of those PUFAs to others varies considerably by the type of oil. With the exception of flaxseed, canola, and soybean oil, the ratio of LA to ALA in vegetable oils is at least 10 to 1. The ratios of LA to ALA for flaxseed, canola, and soy

are approximately 1: 3.5, 2:1, and 8:1, respectively; however, flaxseed oil is not typically consumed in the North American diet. It is estimated that on average in the U.S., LA accounts for 89 percent of the total PUFAs consumed, and ALA accounts for 9 percent. Another estimate suggests that Americans consume 10 times more omega-6 than omega-3 fatty acids.[8] Table 1.2 shows the proportion of omega-3 fatty acids for a number of foods.

Figure 1.1. Classical omega-3 and omega-6 fatty acid synthesis pathways and the role of omega-3 fatty acid in regulating health/disease markers.

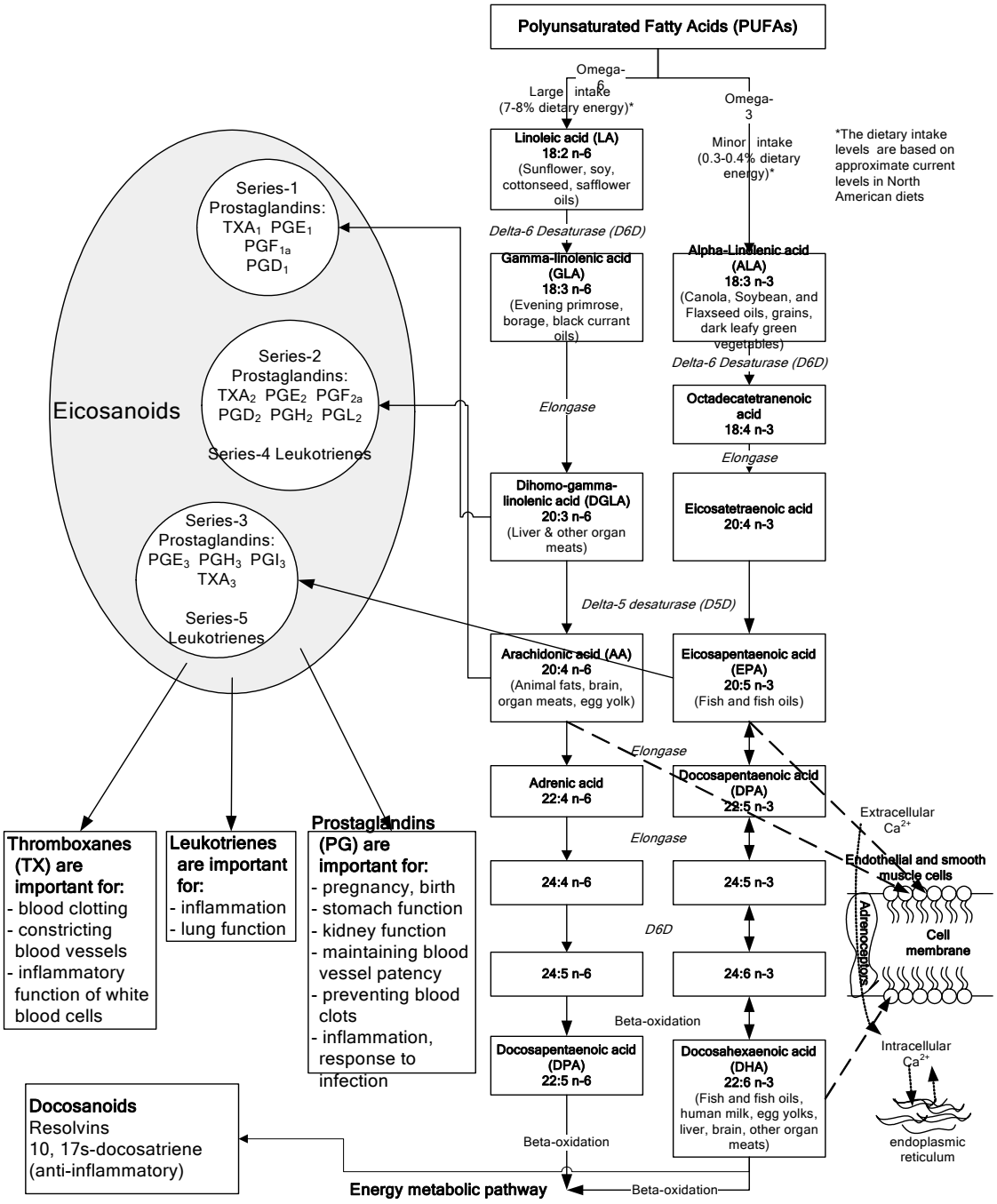


Table 1.2. Sources and proportions of omega-3 fatty acids in common foods and supplements.

Food/supplement	EPA 20:5n-3	DHA 22:6n-3	DPA 22:5n-3	ALA 18:3n-3
Foods/supplements in which total omega-3 fatty acids account for more than 50% of total PUFA				
Fish				
Anchovy	√	√	√	
Halibut	√	√	√	
Herring	√	√	√	
Mackerel	√	√	√	
Salmon	√	√	√	
Sardine	√	√	√	
Tuna				
Canned, waterpacked	√	√	√	
Fresh Bluefin	√	√	√	
Oils/Supplements				
Cod liver oils	√	√	√	
Coromega*	√	√		
Fish oil capsules*	√	√		
Flaxseed/linseed oil*				√
Herring oil	√	√	√	
MaxEPA*	√	√		
Menhaden oil	√	√	√	
Neuromins*		√		
Omacor*	√	√		
Ropufa*	√	√	√	
Salmon oil	√	√	√	
Sardine oil	√	√	√	
Seeds and other foods				
Flaxseeds/Linseeds				√
Spinach, cooked				√
Foods/supplements in which total omega-3 fatty acids are 10-50% of total PUFA				
Oils				
Black currant oil				√
Canola oil†				√
Mustard seed oils				√
Soybean oil				√
Walnut oil				√
Wheat germ oil				√
Other foods				
Wheat germ				√
Human milk‡				√
Foods/supplements in which total omega-3 fatty acids are less than 10% of total PUFA				
Efamol Marine*	√	√		
Peanut butter				√
Soybeans				√
Olive oil				√
Walnuts				√

* Dietary Supplement; † Also called rapeseed oil; ‡ The amounts of ALA, EPA, and DHA in human milk vary greatly as a function of maternal diet; the amount of DHA rarely seems to exceed 25 percent of the total n-3 PUFA content (ALA is present in the greatest amount), but that content as well as the proportion of DHA is assumed to meet the requirements of the infant.

Several lines of research have suggested that the low levels of omega-3 fatty acids currently consumed in the U.S. promote a number of chronic diseases. Whether or not the relatively high intake of omega-6 fatty acids independently contributes to this problem[8] is currently uncertain. Because of the slow rate of elongation and further desaturation of the essential FA, the importance of VLC-PUFAs to many physiological processes, and the overwhelming ratio of LA to ALA in the average U.S. diet, nutrition experts are increasingly recognizing the need for humans to augment the body's synthesis of omega-3 VLC-PUFAs by consuming foods that are rich in these compounds. According to data from two population-based surveys, the major dietary sources of LC 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. The primary dietary sources of omega-6 VLC-PUFAs are meats and dairy products. These surveys, the Continuing Food Survey of Intakes by Individuals 1994-1998 (CSFII) and the third National Health and Nutrition Examination (NHANES III) 1988-94 surveys, are the main sources of dietary intake data for the U.S. population. The CSFII has the advantage of collecting dietary recall data over a period of several days, which may permit estimates of omega-3 intake that more accurately reflect individual intakes than do those of NHANES, which represent 24-hour dietary recalls. However, NHANES intake data have the advantage of being able to be linked to health outcomes. Table 1.3 provides a list of food sources of omega-3 fatty acids.

Table 1.3. Good food sources* of omega-3 fatty acids.

	EPA+DHA	ALA		EPA+DHA	ALA
Fish (3oz. Cooked)			**Oils (1 Tbs.)**		
Anchovy	√		Canola		√
Halibut	√		Cod liver	√	
Herring, Atlantic	√		Flaxseed/linseed		√
Pacific	√		Herring	√	
Mackerel, Atlantic	√		Menhaden	√	
Pacific	√		Salmon	√	
Salmon, Atlantic†	√		Sardine	√	
Sardines	√		Soybean		√
Trout, Rainbow	√		Walnut		√
Tuna, Albacore	√		Wheat germ		√
Canned light, water-packed	√				
Canned white, water-packed	√				
Fresh Bluefin	√				
Organ Meats (3 oz. Cooked)			**Seeds**		
Brain, lamb	√		Flaxseeds/linseeds (1 Tbs.)		√
Brain, pork	√				
Thymus, calf		√			
Other Foods					
Caviar (1 oz.) ‡	√				
Human breast milk (1c) ‡	√§	√			
Soybeans, cooked (1/2c)		√			
Spinach, cooked (1/2c)		√			
Tofu, regular (1/2c)		√			
Walnuts (1/4c)		√			
Wheat germ (1/4c) ‡		√			

Source: Figures adapted from USDA, 2003; * Foods that provide (per serving) 10 percent or more of the Adequate Intake (AI) for ALA or the Acceptable Macronutrient Distribution Range (AMDR) for EPA and DHA (10 percent of the AMDR for ALA); an AI is a recommended average daily intake level based on observed or experimentally determined estimates of nutrient intake by a group of apparently healthy people (thus, assumed to be adequate) when an RDA cannot be determined; an AMDR is defined as "a range of intakes for a particular energy source that is associated with reduced risk of chronic disease while providing adequate intake of essential nutrients."[9]; † Farm-raised Atlantic salmon have nearly identical omega-3 fatty acid levels to wild Atlantic salmon and significantly more omega-3 fatty acids than wild Pacific salmon; ‡ Standard serving size not established; § See table note for Table 1.2.

Table 1.4 shows the mean and median intakes of omega-3 and omega-6 fatty acids reported by NHANES III[i] Table 1.5 shows the mean and median intakes of omega-3 and omega-6 fatty acids reported by CSFII.

Table 1.4. Estimates of the mean intake of LA, ALA, EPA, and DHA in the U.S. population from analysis of NHANES III data.*

	Grams/day		Percent energy intake/day	
	Mean ± SEM	Median (range)†	Mean ± SEM	Median (range)†
LA (18:2n-6)	14.1 ± 0.2	9.9 (0 - 168)	5.79 ± 0.05	5.30 (0 - 39.4)
ALA (18:3n-3)	1.33 ± 0.02	0.90 (0 - 17)	0.55 ± 0.004	0.48 (0 - 4.98)
EPA (20:5n-3)	0.04 ± 0.003	0.00 (0 - 4.1)	0.02 ± 0.001	0.00 (0 - 0.61)
DHA (22:6n-3)	0.07 ± 0.004	0.00 (0 - 7.8)	0.03 ± 0.002	0.00 (0 - 2.86)

*Based on analysis of a single 24-hour dietary recall from NHANES III data; †Distributions are not adjusted for the over-sampling of Mexican –Americans, non-Hispanic African Americans, children five years old and under, and adults 60 years and over in the NHANES III dataset.

Table 1.5. Mean, range, and median usual daily Intakes (ranges) of n-6 and n-3 PUFAs, in the U.S. population, from analysis of CSFII data (1994 to 1998).*

	Mean (gms/d) (± SEM)†	Range of Means (gms/d) (±SEM)	Median (gms/d) (± SEM)†
LA (18:2n-6)	13.0 ± 0.1	6.7 ± 0.1-17.6 ± 0.5	12.0 ± 0.1
Total n-3 FA	1.40 ± 0.01	0.72 ± 0.02 - 1.86 ± 0.04	1.30 ± 0.01
ALA (18:3n-3)	1.30 ± 0.01	0.72 ± 0.02 - 1.73 ± 0.04	1.21 ± 0.01
EPA (20:5n-3)	0.028	0.002 - 0.049	0.004
DPA (22:5n-3)	0.013	0.001 - 0.019	0.005
DHA (22:6n-3)	0.057 ± 0.018	< 0.0005 ± 0.001	0.046 ± 0.013

Source: Adapted from Dietary Reference Intakes Report;[9] *Estimates are based on respondents' intakes on the first day of survey and were adjusted using the Iowa State University method; †For all individuals.

Lacking sufficient evidence from research on the effects or correction of dietary deficiencies to establish Recommended Dietary Allowances (RDAs) for the essential fatty acids, the Food and Nutrition Board (FNB) of the Institute of Medicine[9] has set adequate intakes[ii] (AI) for the essential fatty acids, based on the average intakes of healthy CSFII participants. The AIs for the essential fatty acids vary by age group and sex, as well as for particular conditions such as pregnancy and breastfeeding. For ALA, the AI for men 19 and older, is 1.6 grams/day and the AI for (non-pregnant, non-breastfeeding) women is 1.1 grams/day. The AI for LA is 17 grams/day for men and 11 grams/day for women.

Based on evidence suggesting a role in prevention or treatment of some chronic diseases, the FNB has also established Acceptable Macronutrient Distribution Ranges (AMDR) for the essential fatty acids. An AMDR is defined as "a range of intakes for a particular energy source

[i] The population represented by NHANES III includes individuals ages 2 months and older. Mexican Americans and non-Hispanic African-Americans, children 5 years old and younger, and adults 60 years of age and over were over-sampled to produce more precise estimates for these population groups. There were no imputations for missing 24-hour dietary recall data. A total of 29,105 participants had complete and reliable dietary recall data. The NHANES III also included a physical examination and health survey of each participant.

[ii] An Adequate Intake (AI) is defined as "the recommended average daily intake level based on observed or experimentally determined approximations or estimates of nutrient intake, by a group (or groups) of apparently healthy people, that are assumed to be adequate – used when a recommended dietary allowance cannot be determined."[9] An AI is set when data are insufficient or inadequate to establish an Estimated Average Requirement, on which the RDA is based, and indicate the need for more and better research. The EAR is "the average daily nutrient intake level estimated to meet the requirement of half the healthy individuals in a particular life stage and gender group," based on a specific indicator or criterion of adequacy.

that is associated with reduced risk of chronic disease while providing adequate intake of essential nutrients."[10] The AMDR is expressed as a percentage of total energy intake: The AMDR for LA is set at five to 10 percent of usual energy intake, and the AMDR for ALA is 0.6 to 1.2 percent of energy intake. Of this amount, up to 10 percent can be consumed as EPA and/or DHA, the omega-3 VLC PUFAs. For a person who consumes 2000 kcal/day, ALA intake should range from 1.3 to 2.6 grams/day, and EPA/DHA intake can substitute for 0.13 to 0.26 of that quantity. Table 1.3 lists foods that provide 10 percent or more of these recommended intakes per serving, which may be referred to as "good sources."[iii] Table 1.6 provides the actual omega-3 content per 100 gm for a variety of foods.

[iii] Identifying a food as a "good source" of a nutrient strictly means that one standard serving of the food supplies 10 to 19 percent of the Daily Value for that nutrient. The Daily Values are based on the FDA's Daily Reference Values, standards for the macronutrients (fats, protein, carbohydrates, and dietary fiber), which are similar, although not identical to the DRIs (RDAs) and are based on the amount of energy consumed per day (2000 kcal/d is the reference for calculating DVs). In the case of the PUFAs, no DVs have been established: For this report, the FNB's AIs and AMDRs, have been used instead.

Table 1.6 The omega-3 fatty acid content, in grams per 100 g food serving, of a representative sample of commonly consumed fish, shellfish, fish oils, nuts and seeds, and plant oils.*

Food item	EPA	DHA	ALA	Food item	EPA	DHA	ALA
Fish (Cooked in dry heat unless otherwise specified)				**Fish, continued**			
Anchovy, European	0.8	1.3	-	Tuna, Fresh, Yellowfin	trace	0.2	trace
Bass, Freshwater, Mixed Sp.	0.3	0.5	0.1	Tuna, Light, Canned in Oil	trace	0.1	trace
Bass, Striped	0.2	0.8	trace	Tuna, Light, Canned in Water	trace	0.2	trace
Bluefish	0.3	0.7	-	Tuna, White, Canned in Oil	trace	0.2	0.2
Carp	0.3	0.3	0.3	Tuna, White, Canned in Water	0.2	0.6	trace
Catfish, Channel, farmed	trace	0.1	0.1	Whitefish, Mixed Sp.	0.4	1.2	0.2
Cod, Atlantic	trace	0.2	trace	Whitefish, Mixed Sp., Smoked	trace	0.2	-
Cod, Pacific	0.1	0.2	trace	Wolf fish, Atlantic	0.4	0.4	trace
Eel, Mixed Sp.	0.1	0.1	0.6				
Flounder & Sole Sp.	0.2	0.3	trace				
Grouper, Mixed Sp.	trace	0.2	-	**Shellfish (Raw)**			
Haddock	0.1	0.2	trace	Abalone, Mixed Sp., fried	0.1	0.1	0.1
Halibut, Atlantic and Pacific	0.1	0.4	0.1	Clam, Mixed Sp., moist heat	0.1	0.1	trace
Halibut, Greenland	0.7	0.5	0.1	Crab, Alaska King, moist heat	0.3	0.1	-
Herring, Atlantic	0.9	1.1	0.1	Crab, Blue, moist heat	0.2	0.2	-
Herring, Pacific	1.2	0.9	0.1	Crayfish, Mixed Sp., Farmed	0.1	trace	trace
Mackerel, Atlantic	0.5	0.7	0.1	Lobster, Northern, moist heat	0.1	trace	trace
Mackerel, Pacific and Jack	0.7	1.2	0.1	Mussel, Blue	0.3	0.5	trace
Mullet, Striped	0.2	0.1	trace	Oyster, Eastern, Farmed	0.2	0.2	0.1
Ocean Perch, Atlantic	0.1	0.3	0.1	Oyster, Eastern, Wild	0.3	0.3	0.1
Pike, Northern	trace	0.1	trace	Oyster, Pacific	0.9	0.5	0.1
Pike, Walleye	0.1	0.3	trace	Scallop, Mixed Sp.	0.2	0.2	-
Pollock, Atlantic	0.1	0.5	-	Shrimp, Mixed Sp.	0.2	0.1	trace
Pompano, Florida	0.2	0.5	-	Squid, Mixed Sp., fried	0.2	0.4	0.1
Roughy, Orange	trace	-	trace				
Salmon, Atlantic, Farmed	0.7	1.5	0.1				
Salmon, Atlantic, Wild	0.4	1.4	0.4	**Fish Oils**			
Salmon, Chinook	1.0	0.7	0.1	Cod Liver Oil	6.9	11.0	0.9
Salmon, Chinook, Smoked (lox)	0.2	0.3	-	Herring Oil	6.3	4.2	0.8
Salmon, Chum	0.3	0.5	trace	Menhaden Oil	13.2	8.6	1.5
Salmon, Coho, Farmed	0.4	0.9	0.1	Salmon Oil	13.0	18.2	1.1
Salmon, Coho, Wild	0.4	0.7	0.1	Sardine Oil	10.1	10.7	1.3
Salmon, Pink	0.4	0.6	trace				
Salmon, Pink, Canned	0.8	0.8	0.1				
Salmon, Sockeye	0.5	0.7	0.1	**Nuts and Seeds**			
Sardine, Atlantic, Canned in Oil	0.5	0.5	0.5	Butternuts, Dried	-	-	8.7
Sea bass, Mixed Sp.	0.2	0.6	-	Flaxseed			18.1
Sea trout, Mixed Sp.	0.2	0.3	trace	Walnuts, English	-	-	9.1
Shark, Mixed Sp., battered and fried	0.3	0.4	0.2				
Snapper, Mixed Sp.	0.1	0.3	0.1	**Plant Oils**			
Swordfish	0.1	0.7	0.2	Canola (Rapeseed)	-	-	9.3
Trout, Mixed Sp.	0.3	0.7	0.2	Flaxseed Oil	-	-	53.3
Trout, Rainbow, Farmed	0.3	0.8	0.1	Soybean Lecithin Oil	-	-	5.1
Trout, Rainbow, Wild	0.5	0.5	0.2	Soybean Oil	-	-	6.8
Tuna, Fresh, Bluefin	0.4	1.1	-	Walnut Oil	-	-	10.4
Tuna, Fresh, Skipjack	trace	0.2	-	Wheat germ Oil	-	-	6.9

Source: Figures adapted from USDA, 2003; * Sp = species.

Rationale for and Organization of this Report

Studies show that tissue levels of AA and EPA-derived eicosanoids influence many physiological processes, including calcium transport across cell membranes, angiogenesis, apoptosis, cell proliferation, and immune cell function. These processes are integral to the immune system and hence the pathogenesis of autoimmune disease such as arthritis, systemic lupus erythematosus, and asthma, as well as cancer. Epidemiological studies have suggested that groups of people who consume diets high in omega-3 FAs may experience a lower prevalence of some types of cancer, and many small trials have attempted to assess the effects of adding omega-3 fatty acids to the diet, either as omega-3 FA-rich foods or as dietary supplements (primarily fish oils). In addition, dietary omega-3 FA have been found to modulate tumor formation and proliferation in rodents.

In response to this evidence, a number of omega-3 FA-containing dietary supplements that claim to protect against a variety of conditions have appeared on the market. Thus, AHRQ and the National Institutes of Health (NIH) Office of Dietary Supplements (ODS) have requested a synthesis of the research to date on the health effects of diets rich in omega-3 FA.

The remainder of this report is organized into four chapters. Chapter Two describes the methods we used to identify and review studies related to the role of omega-3 FA in cancer. Specifically, the effects of omega-3 fatty acids on the incidence of cancer, on clinical outcomes after treatment of cancer, and on tumor growth differentiation and apoptosis. Chapter Three presents our findings related to the effects of omega-3 FA on those topics. Chapter Four presents our conclusions and recommendations for future research in this area.

Chapter 2. Methodology

Objectives

The topic of this report was nominated by the National Institutes of Health (NIH) Office of Dietary Supplements (ODS). The three participating Evidence-Based Practice Centers (EPCs) were asked to examine the effects of omega-3 fatty acids, in general, and on the following conditions: Cardiovascular Disease, Transplantation, Immune-Mediated Diseases, Gastrointestinal/Renal Diseases, Cancer, Neurology, Asthma, Child/Maternal Health, Eye Health, and Mental Health. The Southern California EPC (SCEPC) was responsible for examining Immune-Mediated Diseases and Gastrointestinal/Renal Diseases in Year 1 of the project and Cancer and Neurology in Year 2 of the project. This report pertains to cancer.

Scope of Work

The methodology that we used for this study included the following:

- Refining the preliminary questions provided by AHRQ,
- Convening a technical expert panel to advise the SCEPC on the study,
- Identifying sources of evidence in the scientific literature,
- Establishing inclusion/exclusion criteria for the articles identified in the scientific literature,
- Identifying potential evidence with attention to controlled clinical trials using omega-3 fatty acids,
- Evaluating potential evidence for methodological quality and relevance,
- Extracting data from studies meeting methodological and clinical criteria,
- Synthesizing the results,
- Performing further statistical analysis on selected studies,
- Performing pooled analyses where appropriate,

Appendices and Evidence Tables are provided electronically at
http://www.ahrq.gov/clinic/epcindex.htm

- Submitting the results to technical experts for peer review,
- Incorporating reviewers' comments into a final report for submission to AHRQ.

Original Proposed Key Questions

Preliminary questions for the project were developed by ODS in collaboration with the following NIH Institutes: (a) National Cancer Institute (NCI); (b) National Eye Institute (NEI); (c) National Heart, Lung, and Blood Institute (NHLBI); (d) National Institute of Alcohol Abuse and Alcoholism (NIAAA); (e) National Institute of Allergy and Infectious Diseases (NIAID); (f) National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS); (g) National Institute of Child Health and Human Development (NICHD); (h) National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK); (i) National Institute of Mental Health; and (j) National Institute of Neurological Disorders and Stroke (NINDS) The general and disease-specific questions that were originally proposed are detailed in Appendix A.1.

Technical Expert Panel

Each AHRQ evidence report is guided by a Technical Expert Panel (TEP). The TEP advises the SCEPC on refining the preliminary questions, determining the proper inclusion/exclusion criteria for the study and the populations of interest, establishing the proper outcomes measures, and conducting the appropriate analyses.

We convened a TEP that focused specifically on cancer. The TEP was composed of distinguished basic scientists and clinicians, with established expertise in omega-3 fatty acids, human nutrition, dietary assessment methods, cancer biology, and oncology. In addition to the experts that we identified, AHRQ and the relevant NIH Institute(s) recommended a number of industry experts. The members of our technical expert panel and a summary of their key comments and recommendations are listed in Appendix A .2.

Key Questions Addressed in this Report

Based on input from our TEP, the preliminary disease-specific questions were revised. The questions that are addressed in this report are as follows:

Tumor Incidence

- *What is the evidence that omega-3 fatty acids reduce the incidence of tumors?*

If omega-3 fatty acids influence the incidence 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?*
- *What is the evidence that the response to omega-3 fatty acids is dependent 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 dependent 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?*

Identification of Literature Sources

Potential evidence for our study came from three sources: on-line library databases, the reference lists of all relevant articles, and industry experts.

Tumor Incidence and Outcomes After Cancer Treatment

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 3 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. The core search strategy is detailed in Appendix A. Table 4.1.

For the SCEPC, this core search strategy was incorporated into a specific search for cancer. The strategy for this search is detailed in Appendix A. Table 4.2. In consultation with our TEP 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. This search strategy is also outlined in Appendix A. Table 4.2. 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 (3nd 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 (Table A.3.1 and Figure A.3.1).

Tumor Behavior

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. The search strategy is detailed in Appendix A.4. The following databases were searched: Medline, CabHealth, Embase, and Bio-abstracts. 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.

Evaluation of Evidence

Tumor Incidence and Outcomes After Cancer Treatment

Two reviewers independently evaluated the citations and abstracts. Walter Mojica evaluated all of the citations and abstracts; Puja Khanna and Amalia Issa each evaluated a portion of the citations and abstracts.

The reviewers flagged article titles that focused on omega-3 fatty acids and cancer. Language was not a barrier to inclusion. Articles that either reviewer flagged were ordered, as well as those articles in which it was unclear from the title or abstract whether the article was relevant. The articles were ordered from the UCLA library or Infotrieve, a literature retrieval firm with contacts around the world. The literature was tracked using ProCite and Access software.

Two reviewers independently reviewed each article that was ordered to determine whether it should be accepted for further study using structured screening forms (shown in Figure B.1, Appendix B) that included defined sets of inclusion/exclusion criteria (Table A.5.1, Appendix A.5). Walter Mojica reviewed all of the articles; Puja Khanna, Yee-Wei Lim, and Amalia Issa each reviewed a portion of the articles. The reviewers resolved any disagreements by consensus.

Inclusion criteria included 1) description of effects of consumtion of omega-3 fatty acids on a) tumor incidence or b) clinical outcomes after cancer therapy; 2) study design of either a) prospective cohort or b) controlled clinical trial; 3) human study population; 4) description of effect of omega-3 relative to non-exposed people in cohort studies or relative to placebo in controlled clinical trials. There was no language restriction. Although parameters of methodologic quality were evaluated, they were not used as inclusion criteria. We excluded case-control studies because they are highly susceptible to methodologic bias, especially recall bias.

Tumor Behavior

The reviews and meta-analyses on tumor behavior were reviewed by one reviewer, a medical editor and nutritional biochemist with an extensive research background that includes the use of animal and cell culture models.

Extraction of Data

Tumor Incidence and Outcomes After Cancer Treatment

For the articles that passed our screening criteria, two reviewers independently abstracted detailed data onto a specialized quality review form (QRF) (Figure B.2, Appendix B).

Walter Mojica reviewed all of the articles and Puja Khanna and Amalia Issa each reviewed a portion of the articles. We consulted with several outside scientists to complete QRFs for foreign-language articles. The reviewers resolved differences through consensus, and a senior physician researcher resolved any disagreements that could not be resolved through this method.

The QRF included questions 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; and the elapsed time between the intervention and outcome measurements.

Tumor Behavior

Since we planned to conduct a qualitative rather than a quantitative review of the articles about tumor behavior, we did not complete any QRFs for these articles. Walter Mojica screened all of the articles for relevance to this topic, and Sydne Newberry reviewed and summarized the subset of relevant articles on tumor behavior.

Grading Evidence

Methodologic Quality of Randomized Controlled Trials

To evaluate the quality of the design and execution of trials that met our inclusion criteria, we collected information on the QRF about the study design, appropriateness of randomization, blinding, description of withdrawals and dropouts, and concealment of allocation.[11, 12] A score for quality was calculated for each trial using a system developed by Jadad (Appendix A.6, Figure A.6.1).[12] The Jadad score rates studies on a scale of 0 to 5. Empirical evidence has shown that studies scoring 2 or less report exaggerated results compared with studies scoring 3 or more.[13, 14] Thus, studies with a Jadad score of 3 or more are referred to as "high quality," and studies scoring 2 or less are referred to as "poor quality." For our purposes, if a trial was associated with more than one study, its quality score was equal to the maximum score calculated across its associated studies. Additionally, a generic summary quality score (A, B, C) was assigned to each study based upon the combination of its Jadad score and reporting of concealment of allocation (Appendix A.6, Table A.6.1).

Methodologic Quality of Observational Studies

To evaluate the quality of the design and execution of observational studies, we collected information about the validity of ascertainment of cases and exposure, description of withdrawals and dropouts, and adjustment for confounders and blinded assessment of exposure and case status when ascertaining case and exposure status, respectively.[15, 16] A score for quality was not calculated for observational studies, as there is no validated method to do so.

Applicability

In this report, the focus is on the U.S. population. To capture the potential applicability of studies to the different populations of interest as defined in the scope of work (namely Americans with cancer), we categorized the populations in the studies we reviewed in terms of 1) applicability to the U.S. population and 2) health state (Appendix A.6, Table A.6.2). In the

summary tables, each study receives a combined applicability grade consisting of the applicability and health state.

Data Synthesis

We performed both a qualitative and quantitative synthesis of the evidence. We performed a meta-analysis for those studies that sufficiently assessed interventions, populations, and outcomes to justify pooling. Only randomized controlled trials with a placebo comparator group were considered for meta-analysis. For the remaining studies and for those pertaining to the apoptosis, tumor growth, and differentiation question, we performed a qualitative analysis. For the cohort studies that assessed the effects of omega-3 fatty acids on tumor incidence we constructed summary tables for each type of cancer that detailed the age- and multivariate-adjusted risk ratios that were reported for each study arm. These tables are stratified by the specific categories of omega-3 fatty acids for which the risk ratios were reported, i.e. total omega-3, marine omega-3, ALA, EPA or DHA. Also included in these tables are strata for total fish intake which can reasonably be used as a surrogate for omega-3 consumption given the high omega-3 content of fish. Included in these tables is the median intake of the relevant omega-3 fatty acid for each study arm if it was reported. The categories of omega-3 fatty acids that we report are those that were reported in the included studies and were not identical across the different studies. These studies all calculated the intake of different categories of omega-3 fatty acids by comparing the food frequency diaries of study subjects to validated standard tables of nutritional components including omega-3 fatty acids. Total omega-3 intake includes all types of omega-3 fatty acids (ALA, EPA, DHA) that can be obtained from food. Fish intake describes the amount of fish consumed whereas marine omega-3 fatty acids describe the amount of ALA, EPA and DHA derived from marine sources.

Meta-Analysis

Selection of Trials for Descriptive Analysis or Meta-Analysis

First, we identified a set of relevant outcomes, based on input from our TEP. Randomized controlled trials were considered for further analysis if they contained information on a chosen outcome collected within a follow-up interval for which measures were considered clinically comparable.

For some trials, several publications presented the same outcome data. In these cases, we picked the most informative of the duplicates; for example, if one publication was a conference abstract with preliminary data and the second was a full journal article, we chose the latter. The publications dropped for duplicate data do not appear in the evidence table but are noted in the results text. We note that multiple citations of the same article were removed at the title screening stage of the project.

In order for a trial to be included in further analysis, the associated publication(s) had to report on the outcome, and contain sufficient statistical information for the calculation of a summary statistic.

Trial Summary Statistics

Each trial contained one control or placebo group. Some trials contained more than one treatment (omega-3) group. In order not to double-count patients, we chose the most clinically relevant treatment group to enter our analysis, or in some cases combined treatment groups.

For those outcomes that were dichotomous, the summary statistic was a risk ratio, that is, the risk of the outcome in the treatment (omega-3) group divided by the risk of the outcome in the control or placebo group. A risk ratio greater than one indicates that the risk of the outcome in the treatment group is larger than that in the control or usual care arm. For example, if the risk ratio is 1.10, then patients in the treatment group are 1.10 times as likely to have the outcome as those in the control or placebo group.

For each study, we estimated the log risk ratio and its standard deviation. We conducted the analysis on the logarithmic scale for variance-stabilization reasons.[17] We then back-transformed to the risk ratio scale for interpretability.

For those outcomes that were continuous, we extracted the follow-up means and standard deviations for the treatment and control or placebo groups, respectively. If a study did not report a follow-up mean, or a follow-up mean could not be calculated from the given data, the study was excluded from analysis. For studies that did not report a standard deviation or for which a standard deviation could not be calculated from the given data, we imputed the standard deviation by using those studies and groups that did report a standard deviation and weighting all groups equally, or we assumed that the standard deviation was 0.25 of the theoretical range for the specific measure in the study. For example, if a study measured pain on a 0-100 scale, we assumed the standard deviation was 25.

If all studies measured the outcome on the same scale or the measures could all be converted to the same scale, e.g., the summary statistic was the *mean difference* (MD) between the treatment group follow-up mean and the control or placebo group follow-up mean:

Mean difference = treatment follow-up mean – control follow-up mean

We estimated the standard deviation for that mean difference.[18] If the studies used different measurements of the same outcome and we could not convert them all to the same scale, the summary statistic was an effect size. The effect size is the mean difference at follow-up divided by the pooled standard deviation. This summary statistic is unitless and indicates the number of standard deviations by which the treatment and control or placebo group means differ. We estimated an unbiased estimate[19] of Hedges' g effect size[20] and its standard deviation. A negative mean difference or effect size indicates that the treatment is associated with a decrease in the outcome at follow-up as compared with the control or usual care group.

Performance of Meta-Analysis

In some cases, the trials were judged too clinically heterogeneous to combine. Furthermore, for each outcome, condition, and trial stratum combination, we required that at least three trials be available for pooling. In heterogeneous settings and those with insufficient data, we conduct only a descriptive analysis and present the study-level summary statistics but do not estimate a pooled effect.

For those conditions for which trials were determined to be clinically comparable and for which there were at least three trials, we estimated a pooled random-effects estimate[21] by combining summary statistics across trials. We also report the chi-squared test of heterogeneity p-value.[19]

Forest plots were constructed for each setting. Each individual trial summary statistic is shown as a box whose area is inversely proportional to the estimated variance of the summary statistic in that trial. The trial's confidence interval is shown as a horizontal line through the box. The pooled estimate and its confidence interval are shown as a diamond at the bottom of the plot with a dotted vertical line indicating the pooled estimate value. A vertical solid line at one for dichotomous outcomes or at zero for continuous outcomes indicates no treatment effect.

All analyses and drawings of graphs were conducted in the statistical package Stata (Stata Statistical Software: Release 7.0 2001). The only exception was for the analysis of death. Given that deaths were rare, we used exact conditional inference to perform the pooling rather than applying the usual asymptotic methods that assume normality. Asymptotic methods require corrections if zero events are observed, and generally, half an event is added to all cells in the outcome-by-treatment (two-by-two) table in order to allow estimation, because these methods are based on assuming continuity. Such corrections can have a major impact on the results when the outcome event is rare. Exact methods do not require such corrections. We conducted the meta-analysis using the statistical software package StatXact (StatXact 4 for Windows 2000).

Sensitivity Analyses

We conducted post hoc sensitivity analysis for meta-analyses that exhibited significant ($p<0.05$) heterogeneity based on the chi-squared test of heterogeneity. In these sensitivity analyses, we removed the most outlying study chosen based on a visual inspection of the forest plot of the original meta-analysis, and estimated a new pooled estimate. We compared this pooled estimate to the original result as well as observed whether significant heterogeneity still remained.

Publication Bias

We assessed the possibility of publication bias by evaluating a funnel plot of summary statistics for asymmetry, which can result from the nonpublication of small trials with negative

results. These funnel plots include a horizontal line at the fixed-effects pooled estimate and pseudo–95% confidence limits.[22] If bias due to nonpublication exists, the distribution is asymmetric or skewed. Because graphical evaluation can be subjective, we also conducted an adjusted rank correlation test[23] and a regression asymmetry test[22] as formal statistical tests for publication bias. The correlation approach tests whether the correlation between the effect sizes and their variances is significant, and the regression approach tests whether the intercept of a regression of the effects sizes on their precision differs from zero; that is, both formally test for asymmetry in the funnel plot. We acknowledge that other factors, such as differences in trial quality or true study heterogeneity, could produce asymmetry in funnel plots.

Interpretation of the Results

The mean difference pooled results are readily interpretable as they are measured in a clinically interpretable metric. To aid in interpreting the pooled effect size and risk ratio, whenever possible we back-transformed each pooled estimate to a specific metric. In order to do this, we multiplied each pooled effect size estimate by the average standard deviation of the most clinically relevant outcome measured across the trials, e.g., included in the pooled estimate.

Peer Review

This draft report was sent for review to a select group of experts in omega-3 fatty acids, epidemiology, nutrition, and cancer. The names, expertise, and affiliations of the peer reviewers are listed in Table A.7.1, Appendix A. Additionally, this draft report was sent to the members of the TEP for review. Service as a peer reviewer or as a technical expert panelist does not imply agreement or endorsement of the findings of this report.

Chapter 3. Results

Results of Literature Search

Tumor Incidence and Outcomes After Cancer Treatment

Figure 3.1 displays the flow of the literature review to assess the effects of omega-3 FA on tumor incidence and treatment.

To assess the effects of omega-3 FA on tumor incidence and treatment, the University of Ottawa EPC e-mailed us a total of 4,729 citations as a result of their computerized library searches; our reviewers found 93 additional citations after reference mining; a request for unpublished data yielded one citation; peer reviewers of a draft of this report identified 11 more citations. In total we reviewed 4,834 citations. Our reviewers considered 1,238 of these article titles to be relevant to our research topics. We were able to retrieve 1,210 (98%) of these articles.

Of the articles retrieved, 356 were accepted for further review because they reported on results from randomized clinical trials, controlled clinical trials, or prospective cohort studies of omega-3 FA in the treatment of cancer. We rejected 854 at this stage: 283 were reviews and meta-analyses, 328 reported on a topic other than omega-3 FA, 112 did not report on a population of interest, 26 had descriptive study designs, 89 had other inappropriate study designs, 14 either reported on a condition other than those of interest or did not describe the effect of omega-3 FA on these outcomes, and two were written in foreign languages for which we did not have translators.

Of the 356 articles that went to further review, a total of 263 were rejected. Among those rejected, we were unable to compare the effect of omega-3 FA across study arms in 39. The remaining 224 were rejected for study design (i.e., case control/case series). Thus, a total of 93 articles were tentatively accepted for supplementary analysis. However, on further inspection, 41 of these articles did not report on outcomes of interest and/or we were not able to compare the effects of omega-3 FA across study arms, leaving 52 articles for the final analysis. Of these 52, 33 reported on cancer incidence and 19 reported on cancer treatment. Of the 19 articles that reported on cancer treatment, all reported on cancer surgery; none reported on chemotherapy or radiation therapy. Some articles assessed more than one cancer surgery outcome: 14 assessed post-operative complications, 13 assessed length of stay, 10 assessed mortality, 11 assessed nutrition, and three assessed body weight.

As noted above, an additional 11 articles not identified in our initial search were recommended by external reviewers who reviewed a first draft of this report. Among those studies, 3 met our inclusion criteria and were added to the report.

Tumor Behavior

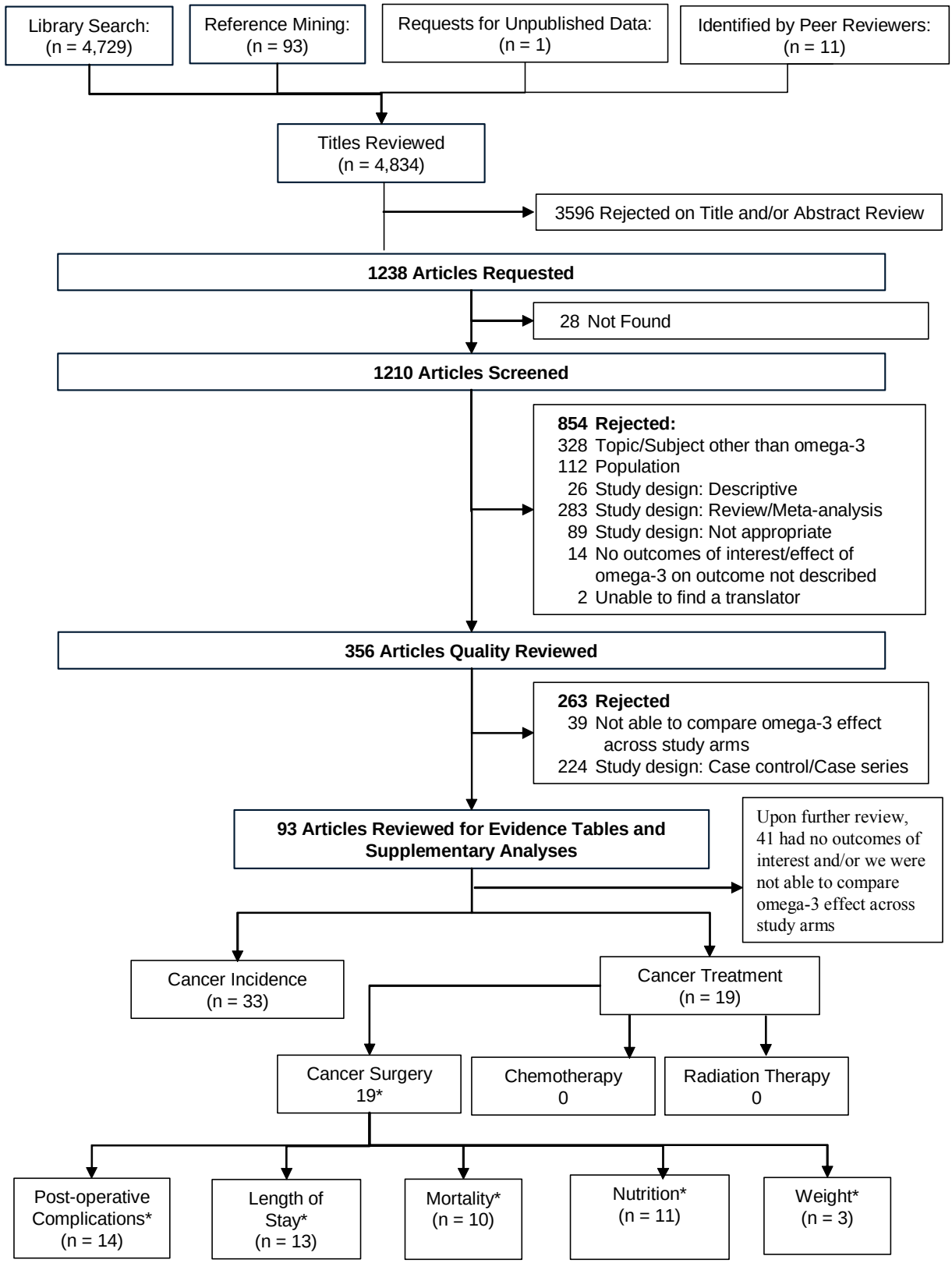
Figure 3.2 displays the flow of the literature reviews to assess the effects of omega-3 FA on tumor growth, differentiation, and apoptosis.

To assess the effects of omega-3 FA on tumor growth differentiation and apoptosis, the University of Ottawa EPC e-mailed us a total of 366 citations as a result of their computerized library searches, and our reviewers found three citations after reference mining, for a total of 369 citations. Our reviewers considered 82 of these article titles to be relevant to our research topics. We were able to retrieve 60 (73%) of these articles.

Of the 60 articles retrieved, 27 were accepted for further review, because they appeared to report on the effects of omega-3 FA (added to the diet or to cell cultures) on cancer development, apoptosis, or cell differentiation in laboratory animals or cell culture systems. The other 37 articles were rejected because they did not report on a topic of interest (26), were not about omega-3 FA (7), were not about supplementation (1), were about other mechanisms (2), were reviews (1), or were not about cancer development (1).

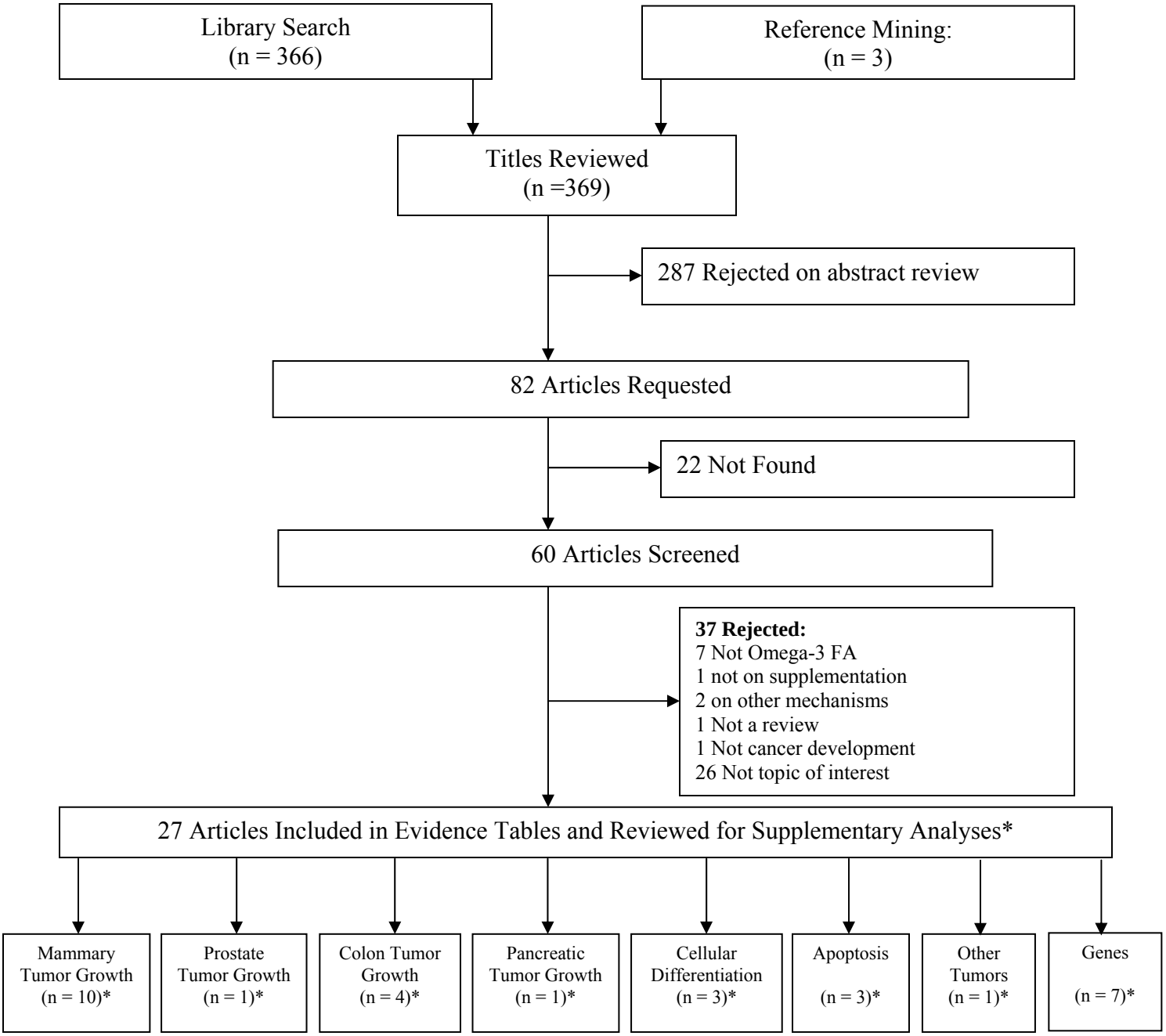
Summaries of the 27 accepted articles can be found in Appendix C. Table C.3.1 summarizes the findings for the systematic reviews and meta-analyses, and Table C.3.2 summarizes the findings for the nonsystematic reviews of tumor growth. Table C.3.3 summarizes the findings relevant to differentiation. Table C.3.4 summarizes the findings regarding apoptosis. Table C.3.5 summarizes the evidence related to a role for n-3 transport and metabolic enzyme genes. These findings are described qualitatively below as responses to the questions posed.

Figure 3.1. Literature flow to assess the effects of omega-3 FA on tumor incidence and treatment.



* Some articles assessed more than one outcome.

Figure 3.2. Literature flow to assess the effects of omega-3 FA on tumor behavior.



* Some articles assessed more than one outcome

Tumor Incidence

We identified 33[24-56] reports that described the effect of omega-3 FA on the incidence of eleven different types of cancer among subjects enrolled in nineteen different cohorts (Table 3.1). Over half of these reports described the effect of omega-3 FA on one of three types of cancer: breast,[37, 41, 43, 44, 51, 52, 55] colorectal,[30, 34, 38, 40, 46, 54] and prostate.[27, 28, 29, 39, 50, 53, 57] The remaining publications described the effects of omega-3 FA on the incidence of eight different types of cancer with only one or two publications describing the effects on each of these types of cancer.

Cohort Characteristics

The characteristics of the nineteen cohorts in which cancer incidence was studied are summarized in Table 3.2. These cohorts ranged in size from 6,000 to 121,000, with from 9,000 to 1.5 million person-years of observation; together, these cohorts include over 700,000 subjects and 3 million person-years of observation. The observation periods in these cohorts ranged from 3 to 30 years.

Demographic characteristics differ greatly across these cohorts. Among the cohorts, eleven comprise subjects who live in countries outside the US, and seven comprise US residents. Among both foreign and US cohorts, seven are population-based (Table 3.2), although from populations that are racially and culturally distinct. For example, while the Aichi Prefecture Cohort[24] and the Netherlands Cohort[37, 38] are both population-based samples, the former comprises Asians from rural Japan, the latter Caucasians from Northern Europe. None of the US cohorts are derived from a population-based sample. The remaining eleven cohorts were drawn from base populations with specific geographic, professional, religious and/or other socioeconomic characteristics. For example, the Health Professionals Follow-up study cohort comprises US male dentists, optometrists, osteopaths, podiatrists, pharmacists, and veterinarians - professionals who are highly educated and generally of high income. Subjects in the Seventh-day Adventist Cohort study cohort are, as the name suggests, members of the Seventh-day Adventist Church, which advocates a healthy lifestyle[58] that includes abstinence from alcohol, coffee, tea, and tobacco; many are vegetarians who supplement their diet with eggs and milk.[59] These and other unique measured and unmeasured characteristics of the cohorts could differentially affect the risk estimates presented by each study. However, reproduction of findings across these diverse cohorts would strengthen their validity.

Particularly relevant to this report, the range of omega-3 consumption varies among the different cohorts. Figures 3.3 to 3.7 display the population intake of different categories of omega-3 fatty acid consumption for the cohorts that are described in this report. Each figure describes a different category of omega-3 fatty acid consumption and includes a series of stacked bars for each cohort that signify the amount consumed for quintiles, quartiles, or tertiles of intake. Each bar bounds the range of intake for a quintile, quartile, or tertile. In order to demonstrate how omega-3 consumption in the cohorts identified for this report compare to US population norms, Figures 3.5 to 3.7 additionally indicate the mean US consumption of ALA, EPA, and DHA, respectively, as reported by NHANES III and CSFII.

Because the types of omega-3 fatty acid assessed varied across the cohorts, it is not possible to determine which cohort had the highest or lowest omega-3 fatty acid consumption. However,

among cohorts for which fish intake was reported, the highest population intake was reported for the Lifespan Study cohort, for which the median intake of fish in the lowest and highest tertiles were less than one serving per week and greater than 5 servings per week, respectively. The lowest intake was reported in the Seventh Day Adventist cohort, for which the median intake of fish is estimated to be 1 serving per week. In general, omega-3 fatty acid intake in the US cohorts was not very different than for Asian and European cohorts (Figures 3.3 to3.7). Among US cohorts, the Health Professionals Follow-up Study reported a median ALA intake similar to that reported by NHANES III and CSF II; intake in the Nurses Health Study Cohort was a bit lower than that reported but CSF II, but similar to that reported by NHANES II (Figure 3.5). Among foreign cohorts, median ALA intake in the Netherlands Cohort study was similar to that reported by NHANES III and CSF II; intake was lower in the Swedish Mammography cohort (Figure 3.5). Median intake of EPA and DHA were much higher in the Netherlands and Swedish Women Mammography cohorts than that reported by NHANES III and CSFII (Figures 3.6 and 3.7). The amount of omega-3 fatty acid in the diet of different populations could differentially affect risk estimates, depending on the mechanism of action and/or dose-response of the effects of omega-3 FA on cancer. If omega-3 FA have no effect on cancer, then the amount of omega-3 FA in the diets of various populations should not affect risk estimates. If omega-3 FA do affect cancer risk, then the amount of omega-3 FA in the diets of different populations could have several effects on risk estimates. Assuming a linear dose-response to omega-3 FA, then a dose effect over different levels of intake should be seen for all cohorts regardless of the mean consumption of the population. Assuming a threshold effect at a low dose, an effect might not be observed for cohorts in which most subjects consume at least the threshold dose. Conversely, assuming a threshold effect at a high dose, an effect might not be observed for cohorts in which most subjects do not consume at least the threshold dose.

Other factors that should be considered when interpreting the data from the different cohorts include the year of birth for the members of the cohort and when the exposure to omega-3 FA was assessed. Many of the cohorts comprise individuals born between 1915 and 1935, a few comprise individuals born before 1925, and a few include a broad range of birth years ranging roughly from 1910 to1960 (Table 3.2). It is possible that secular trends, including changes in diet, could differentially affect risk estimates for different birth cohorts. It is likely that the diets of individuals in the 1915 to 1935 birth cohorts, particularly those from Europe and Japan, were affected for a period of time by World War II. For all but two of the cohorts, exposure to omega-3 FA was assessed at one time point. In most studies, dietary habits during a finite preceding time period of up to one year were assessed at the time of enrollment. In contrast, the Health Professionals Follow-up Study and the Nurses' Health Study assessed dietary habits at multiple time points.

Summaries of all evaluated studies can be found in Appendix C.1. The following sections describe the reported effects of omega-3 FA and the incidence of specific types of tumors.

Overall Effect of Omega-3 FA on Tumor Incidence

The risk ratios for developing cancer for the highest consumption group (quartile, quintile, dose group, etc) relative to the lowest consumption group for fish consumption, total omega-3 FA consumption, ALA consumption, DHA consumption, and EPA consumption are displayed in

Figures 3.8 through 3.12. Among 44 estimates of association calculated across 19 different cohorts for 11 different types of cancer and 5 different ways to assess omega-3 FA consumption, only six are statistically significant. Significant associations between omega-3 FA consumption and cancer risk were reported for lung cancer in two studies; for breast cancer in two; 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. Likewise for breast cancer, one of the statistically significant risk ratios was for increased risk and one was for decreased risk; five other risk ratios did not show a significant association. Only one study assessed skin cancer risk. Hence, no trend was found across many different cohorts and many different categories of omega-3 FA consumption to suggest that omega-3 FA reduce overall cancer risk.

Table 3.1. Prospective observational studies of cancer incidence by cancer type and cohort.

Cohort	Cancer Type										
	Aerodigestive, upper	Bladder	Breast	Colorectal	Lung	Lymphoma, Non-hodgkin's	Ovarian	Pancreatic	Prostate	Skin, BCC	Stomach
Aichi Prefecture Cohort, Japan					Takezaki, 2003[24]						
Alpha-tocopherol, Beta-Carotene Cancer Prevention Study								Stolzenberg-Solomon, 2002[25]			
Diet, Cancer and Health Study			Stripp, 2003[55]								
Fukuoka Prefecture Cohort, Japan											Ngoan, 2002[26]
Hawaii Health Surveillance Program									LeMarchand, 1994[27]		
Health Professionals Follow-up Study				Giovannucci, 1994[30]					Giovannucci, 1993[29]; Augustsson, 2003;[28] Leitzman, 2004[57]	Van Dam, 2000[31]	
Honolulu Heart Program	Chyou, 1995[32]	Chyou, 1993[33]									
Iowa Women's Health Study				Bostick, 1994[34]		Chiu, 1996[35]					
Japan Collaborative Cohort					Ozasa, 2001[36]						
Life Span Study			Key, 1999[52]								
Netherlands Cohort Study			Voorips, 2002[37]	Goldbohm, 1994[38]					Schuurman, 1999[39]		

Table 3.1 (continued). Prospective observational studies of cancer incidence by cancer type and cohort.

Cohort	Cancer Type										
	Aerodigestive, upper	Bladder	Breast	Colorectal	Lung	Lymphoma, Non-hodgkin's	Ovarian	Pancreatic	Prostate	Skin, BCC	Stomach
New York University Women's Health Study				Kato, 1997[40]							
Norwegian National Health Screening Service Cohort			Vatten, 1990[41]		Veierod, 1997[42]						
Norwegian Cohorts					Kvale, 1983[56]						
Nurses' Health Study			Holmes 1999[44]; Holmes, 2003[43]	Willett, 1990[46]		Zhang, 1999[47]	Bertone, 2002[48]	Michaud, 2003[49]			
Seventh-day Adventist									Mills, 1989[50]		
Singapore Chinese Health Study			Gago-Dominguez, 2003[51]								
Swedish Twin Registry									Terry, 2001[53]		
Swedish Women in Mammography Screening Program				Terry, 2001[54]							

Table 3.2. Characteristics of cohorts that have described the effects of omega-3 FA on cancer incidence.

Cohort	Author, year	Cancer type	# subjects in cohort*	Birth years	Enrollment period	Observation period, exposure to omega-3	Ascertainment of omega-3 exposure	Observation period, cancer	Ascertainment of cancer	Base-population	Predominant race/ethnicity	Gender(s) in cohort
Aichi Prefecture Cohort, Japan	Takezaki, 2003[24]	Lung	9,753	1917-1972	1986-1989	Enrollment	Food frequency questionnaire	ND	ND	Population of Aichi Prefecture	Japanese	
Alpha-tocopherol, Beta-Carotene Cancer Prevention Study	Stolzenberg-Solomon, 2002[25]	Pancreatic	27,111	1916-1938	1985-1988	Enrollment	Food frequency questionnaire about 1-year prior to enrollment	1985-1997	Tumor registry with medical records verification	Male smokers	Caucasian	Male
Diet, Cancer and Health Study	Stripp, 2003[55]	Breast	29,875	1929-1947	1993-1997	Enrollment	Food frequency questionnaire	1993-2000	Cancer registry	Population of greater Copenhagen and Aarhus	Caucasian	Male and Female Female for substudy reported here
Fukuoka Prefecture Cohort, Japan	Ngoan, 2002[26]	Stomach	13,250	1880-1974	1986-1989	Enrollment	Dietary questionnaire	Not stated	Not explicitly stated; infer death certificates from text.	Population of Fukuoka Prefecture	Japanese	Male and Female
Hawaii Health Surveillance Program	LeMarchand, 1994[27]	Prostate	8,881	ND	1975-1980	1975-1980	Lifestyle questionnaire	1975-1989	Hawaii tumor registry	Hawaiians of Japanese, Caucasian, Filipino, Hawaiian or Chinese ancestry	Caucasian, Asian, Pacific Islander	Male
Health Professionals Follow-up Study	Augustsson, 2003[28]	Prostate	51,529	1911-1946	1986	1986, 1990, 1994	Food frequency questionnaire	1986-1998	self-report or vital records confirmed by medical records review	Male dentists, optometrist, osteopaths, podiatrists, pharmacists, and veterinarians that responded to a postal questionnaire	Caucasian	Male
	Giovannucci, 1993[29]	Prostate										
	Giovannucci, 1994[30]	Colorectal										
	Leitzmann, 2004[57]	Prostate										
	VanDam, 2000[31]	Skin, basal cell carcinoma										

* Total number of subjects enrolled in cohort, number may differ from number of subjects in analyses of specific diseases.

Table 3.2 (continued). Characteristics of cohorts that have described the effects of omega-3 FA on cancer incidence.

Cohort	Author, year	Cancer type	number subjects in cohort*	Birth years	Enrollment period	Observation period, exposure to omega-3	Ascertainment of omega-3 exposure	Observation period, cancer	Ascertainment of cancer	Base-population	Predominant race/ethnicity	Gender(s) in cohort
Honolulu Heart Program	Chyou, 1995[32]	Upper Aero-digestive	8,006	1900-1919	1965-1968	1965-1968	Food frequency questionnaire and 24-hr diet recall history	1965-1993	Oahu hospitalizations for cancer and Hawaii Tumor Registry†	Institutionalized American men of Japanese ancestry residing on Oahu.	Hawaiians of Japanese ancestry	Male
	Chyou, 1993[33]	Bladder										
Iowa Women's Health Study	Bostick, 1994[34]	Colorectal	41,837	1917-1931	1986	1986	Food frequency questionnaire re: prior 1-year	1986-1992	State Health Registry of Iowa	Women with valid Iowa driver's license	Caucasian	Female
	Chiu, 1996[35]	Non-Hodgkin's lymphoma										
Japan Collaborative Cohort	Ozasa, 2001[36]	Lung	110,792	1909-1950	1988-1990	At enrollment	Food frequency questionnaire	1988-1997	Death certificates	Population of 19 prefectures in Japan	Japanese	Male and Female
Life Span Study	Key, 1999[52]	Breast	Approx. 120,000	NR	1969-1970	1969-1970, 1979	Food frequency questionnaire	1969-1993, 1981-1983	Hiroshima and Nagasaki cancer Registries	Survivors of atomic bomb in Hiroshima or Nagasaki, Japan that were alive on September 1, 1969	Asian	Male and Female
Netherlands Cohort Study	Voorrips, 2002[37]	Breast	62,573	1917-1931	1986	1986	Food frequency questionnaire	1986-1992	Regional cancer registries	Population	Caucasian/ Dutch	Male and female
	Goldbohm, 1994[38]	Colorectal										
	Schuurman, 1999[39]	Prostate										
New York University Women's Health Study	Kato, 1997[40]	Colorectal	14,727	1920-1957	1985-1991	At enrollment	Dietary questionnaire	1985-1992	Self report confirmed by medical records review supplemented by review of state cancer registries and National Death index	Women treated at the Guttman Breast Diagnostic Institute in New York City or at the Strax Breast Cancer Institute in Florida	Caucasian, Black, Hispanic	Female
Norwegian Cohorts	Kvale, 1983[56]	Lung	16,713	NR	1964	One- time questionnaire between 1967 and 1969	Dietary questionnaire	From questionnaire until 1978	Cancer registry	Population	Caucasian	Male and Female
Norwegian National Health Screening Service Cohort	Vatten, 1990[41]	Breast	14,729	1925-1942	1974-1977	At enrollment	Food frequency questionnaire and 24-hr diet recall history	11-14 years f/u, mean = 12	National Cancer Registry	Population of Norway	Caucasian	Male and Female
	Veierod, 1997[42]	Lung										

* Total number of subjects enrolled in cohort, number may differ from number of subjects in analyses of specific diseases ; † Part of NCI SEER Program.

Table 3.2 (continued). Characteristics of cohorts that have described the effects of omega-3 FA on cancer incidence.

Cohort	Author, year	Cancer type	# subjects in cohort*	Birth years	Enrollment period	Observation period, exposure to omega-3	Ascertainment of omega-3 exposure	Observation period, cancer	Ascertainment of cancer	Base-population	Predominant race/ethnicity	Gender
Nurses' Health Study	Holmes, 2003[43]	Breast	121,700	1921-1946	1976	1980, 1984, 1986, 1990, 1994	Food frequency questionnaire re: prior 1-year	1980-1994	Self-report or vital records confirmed by medical records review	US female registered nurses	Caucasian	Female
	Holmes, 1999[44]	Breast										
	Willett, 1990[46]	Colorectal										
	Zhang, 1999[47]	Non-Hodgkin's lymphoma										
	Bertone, 2002[48]	Ovarian										
	Michaud, 2003[49]	Pancreatic										
Seventh-day Adventist	Mills, 1989[50]	Prostate	ND	ND	1976	1976	Lifestyle questionnaire	1976-1982	Self-report confirmed by medical records review and Cancer registry	Seventh-day Adventist households in California	ND	Male and Female

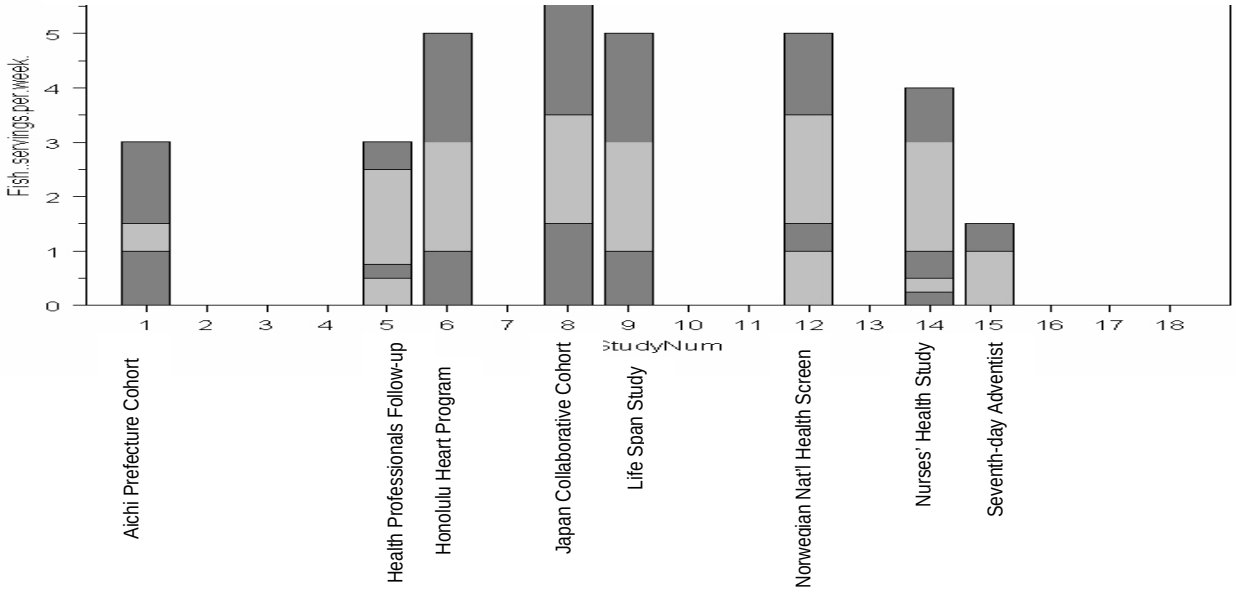
* Total number of subjects enrolled in cohort, number may differ from number of subjects in analyses of specific diseases.

Table 3.2 (continued). Characteristics of cohorts that have described the effects of omega-3 FA on cancer incidence.

Cohort	Author, year	Cancer type	# subjects in cohort*	Birth years	Enrollment period	Observation period, exposure to omega-3	Ascertainment of omega-3 exposure	Observation period, cancer	Ascertainment of cancer	Base-population	Predominant race/ethnicity	Gender
Singapore Chinese Health Study	Gago-Dominguez, 2003[51]	Breast	63,257	1919-1953	1993-1998	1-year prior to enrollment	Food frequency questionnaire	Enrollment - 2000	Singapore Cancer registry	Permanent residents or citizens of Singapore living in government housing estates† speaking Hokkien or Cantonese	Asian	Male and Female
Swedish Twin Registry	Terry, 2001[53]	Prostate	6272	1886-1925	1961	1967	Lifestyle questionnaire	1967-1997	National Cancer and death registries	Male twin pairs residing in Sweden in 1961	Caucasian	Male
Swedish women in mammography-screening program	Terry, 2001[54]	Colorectal	61,463	1925-1939	1987-1990	6-months prior to enrollment	Food intake questionnaire	Enrollment-1998	Regional cancer registries	Participants of population-based mammography screening program	Caucasian	Female

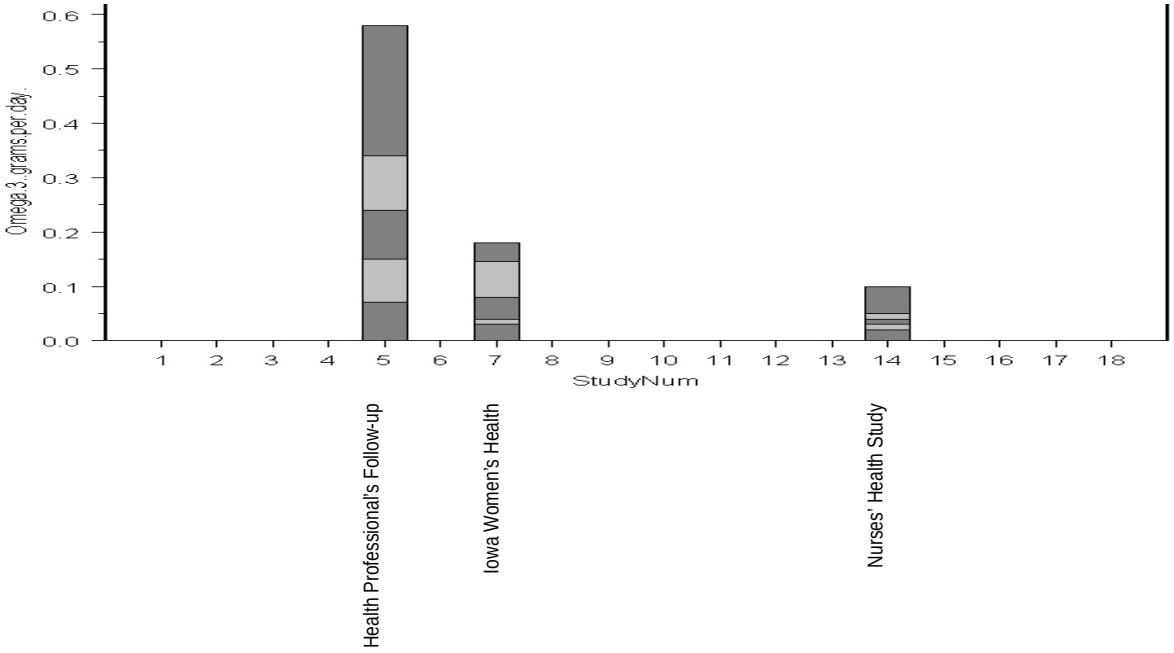
* Total number of subjects enrolled in cohort, number may differ from number of subjects in analyses of specific diseases; † 86% of population lived in this type of housing at the time the cohort was formed.

Figure 3.3. Distribution of fish consumption by cohort relative to US intake reported in CSFII and NHANES III.*



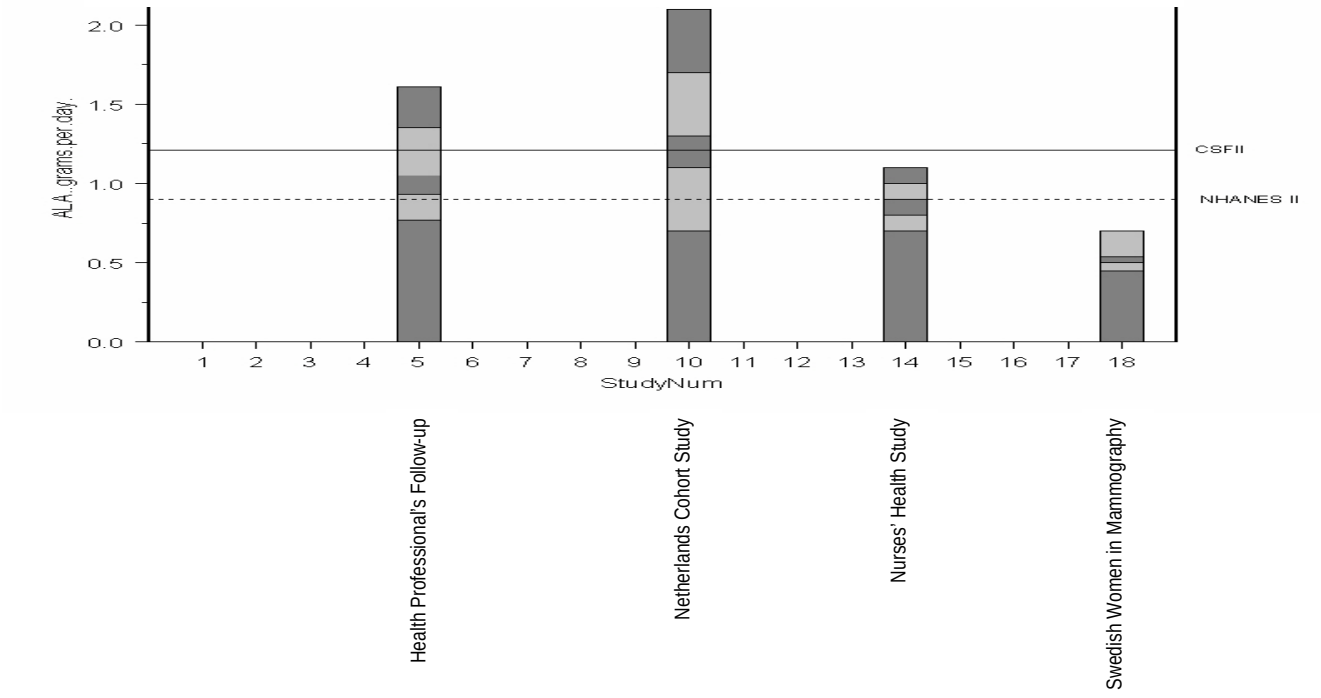
* The stacked bars for each cohort represent the range of fish consumption for the quintiles, quartiles or tertiles of fish consumption for that cohort.

Figure 3.4. Distribution of omega-3 consumption by cohort relative to US intake reported in CSFII and NHANES III.*



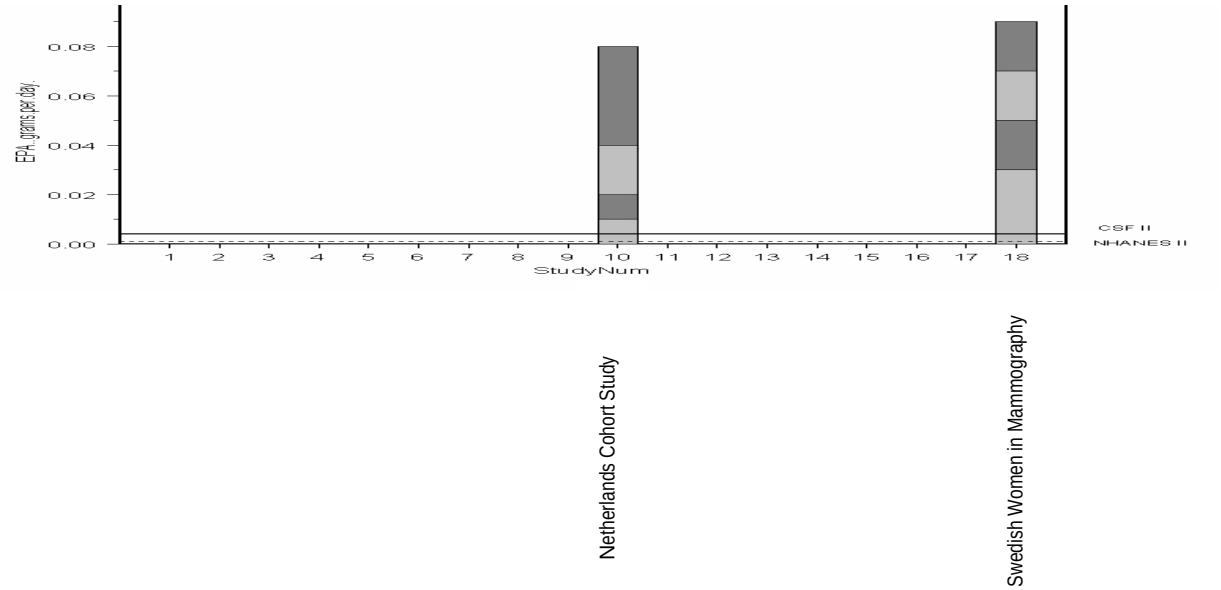
*The stacked bars for each cohort represent the range of omega-3 fatty acid consumption for the quintiles of omega-3 fatty acid consumption for that cohort.

Figure 3.5. Distribution of ALA consumption by cohort relative to US intake reported in CSFII and NHANES III.*



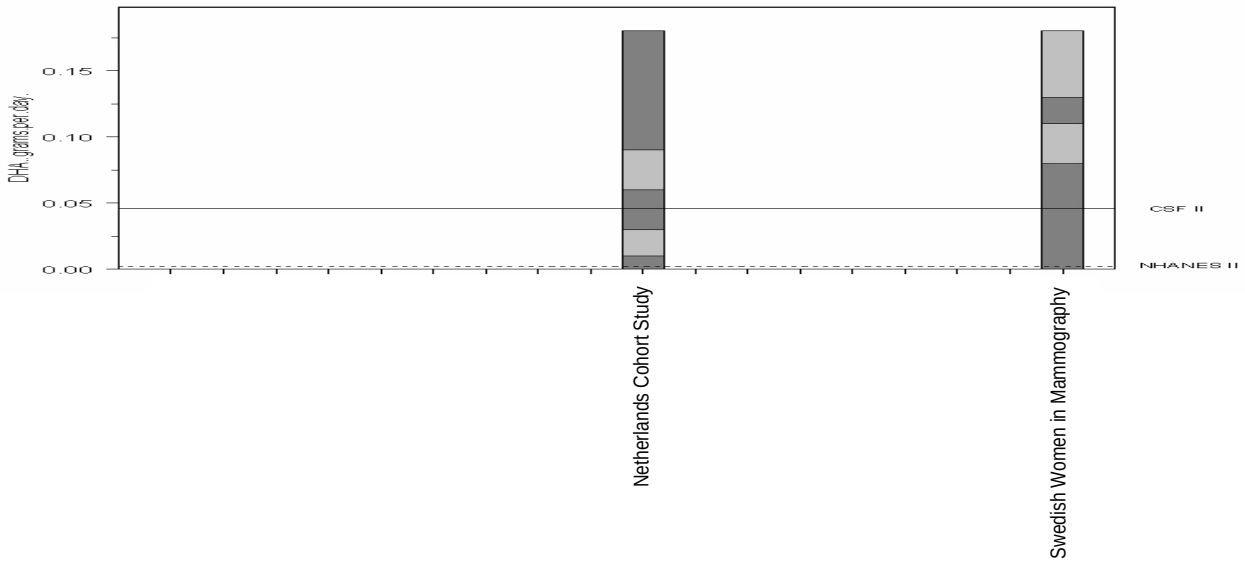
*The stacked bars for each cohort represent the range of ALA consumption for the quintiles or quartiles of ALA consumption for that cohort; CSFII = Mean U.S. intake as measured by the Continuing Food Survey of Intakes by Individuals 1994-1998; NHANES III = Mean U.S. intake as measured by the third National Health and Nutrition Examination 1988-1994.

Figure 3.6. Distribution of EPA consumption by cohort relative to US intake reported in CSFII and NHANES III.*



*The stacked bars for each cohort represent the range of EPA consumption for the quartiles of EPA consumption for that cohort; CSFII = Mean U.S. intake as measured by the Continuing Food Survey of Intakes by Individuals 1994-1998; NHANES III = Mean U.S. intake as measured by the third National Health and Nutrition Examination 1988-1994.

Figure 3.7. Distribution of DHA consumption by cohort relative to US intake reported in CSFII and NHANES III.*



* The stacked bars for each cohort represent the range of DHA consumption for the quintiles or quartiles of DHA consumption for that cohort; CSFII = Mean U.S. intake as measured by the Continuing Food Survey of Intakes by Individuals 1994-1998; NHANES III = Mean U.S. intake as measured by the third National Health and Nutrition Examination 1988-1994.

Figure 3.8. Risk of developing cancer for subjects with the highest grouping of fish intake relative to subjects with the lowest grouping of intake by cancer type.

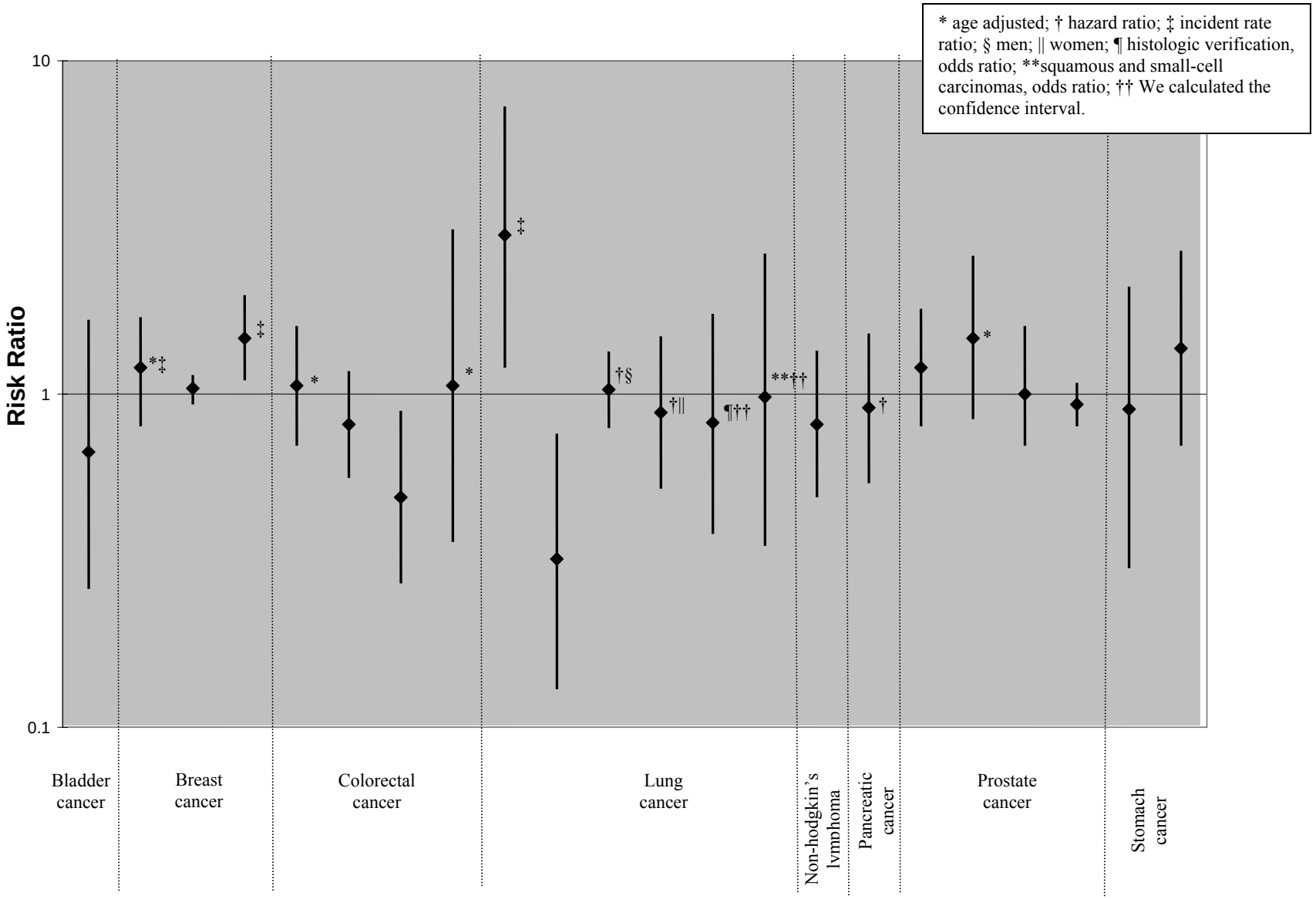


Figure 3.9. Risk of developing cancer for subjects with the highest grouping of omega-3 intake relative to subjects with the lowest grouping of intake by cancer type.

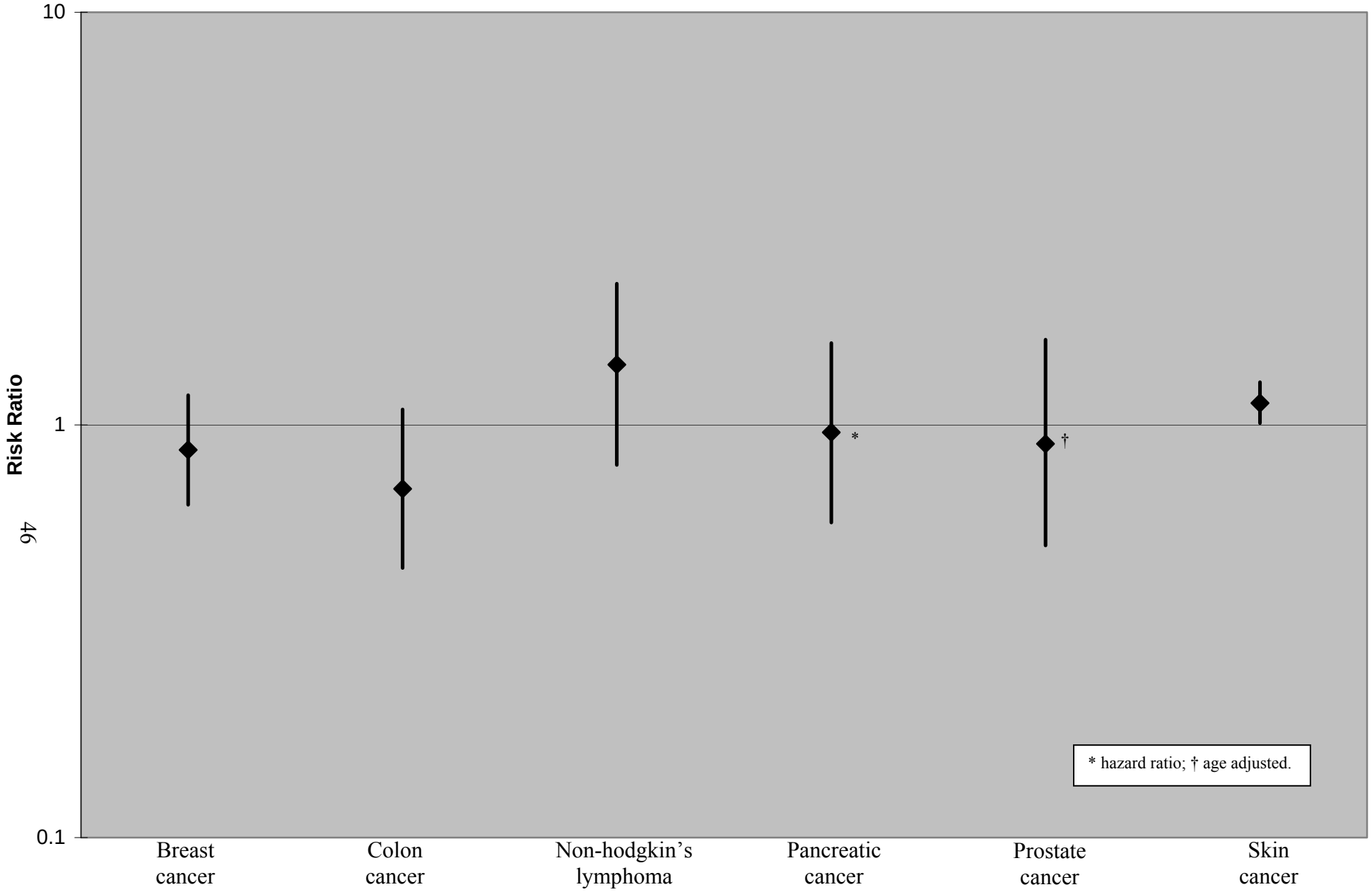


Figure 3.10. Risk of developing cancer for subjects with the highest grouping of ALA intake relative to subjects with the lowest grouping of intake by cancer type.

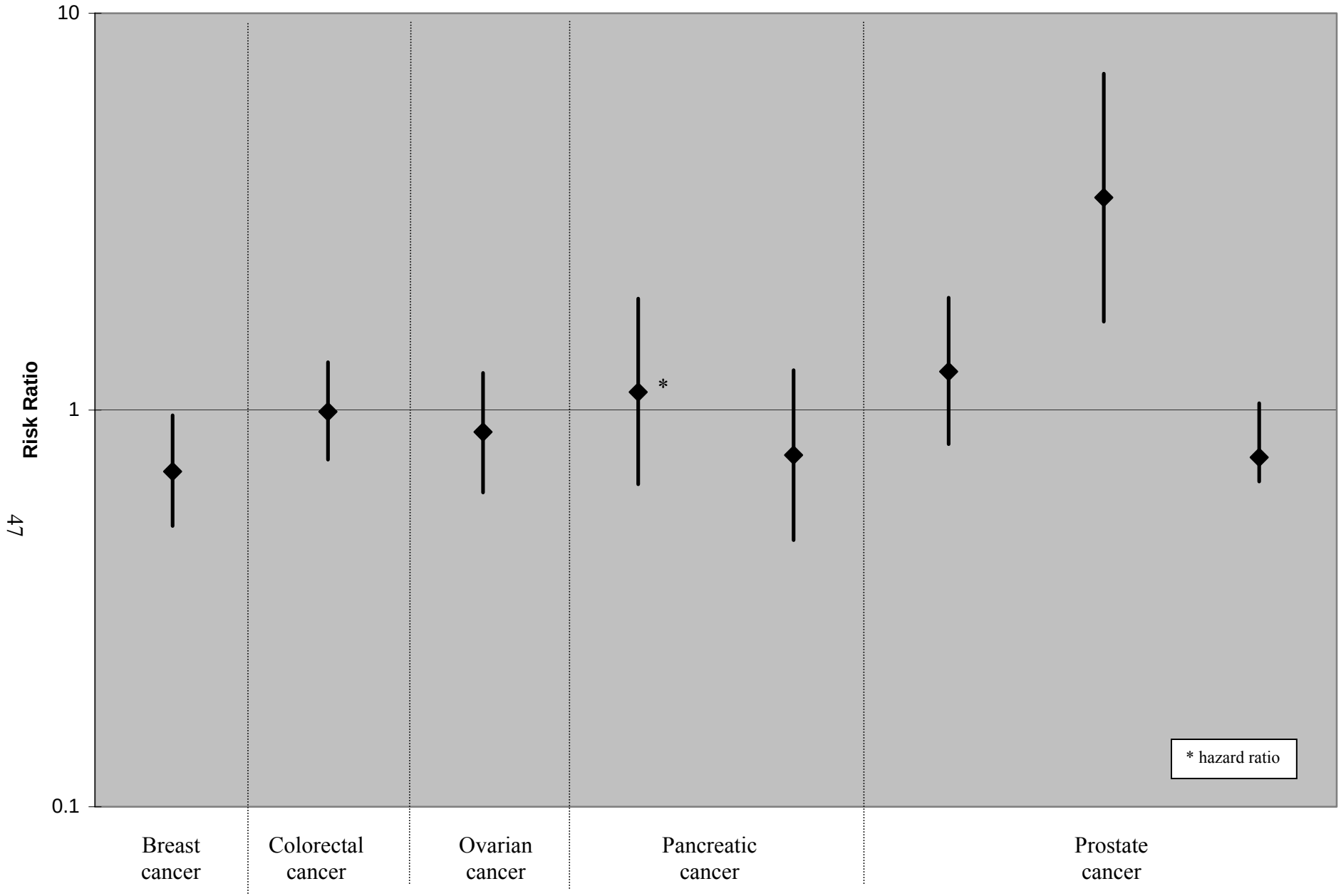


Figure 3.11. Risk of developing cancer for subjects with the highest grouping of EPA intake relative to subjects with the lowest grouping of intake by cancer type.

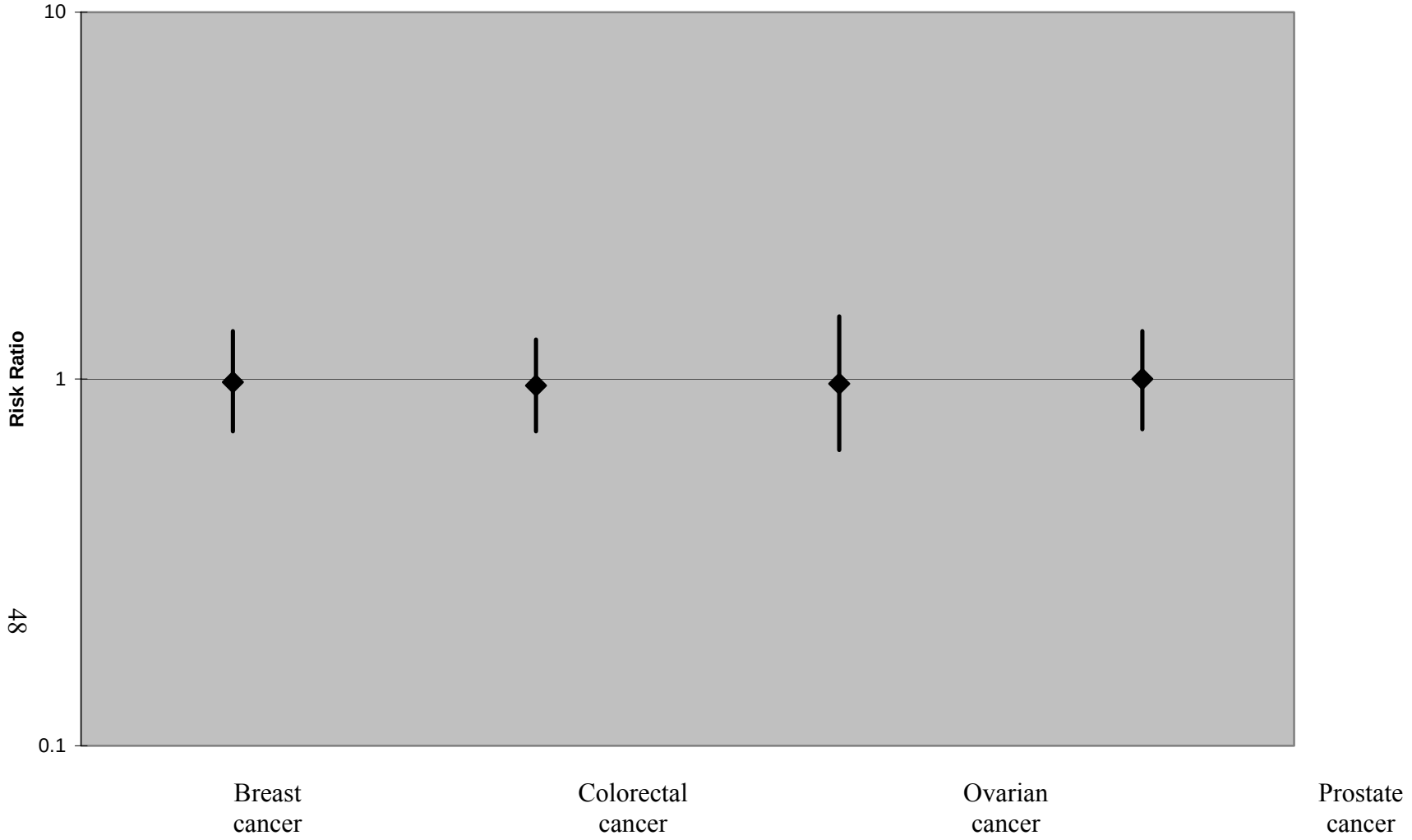
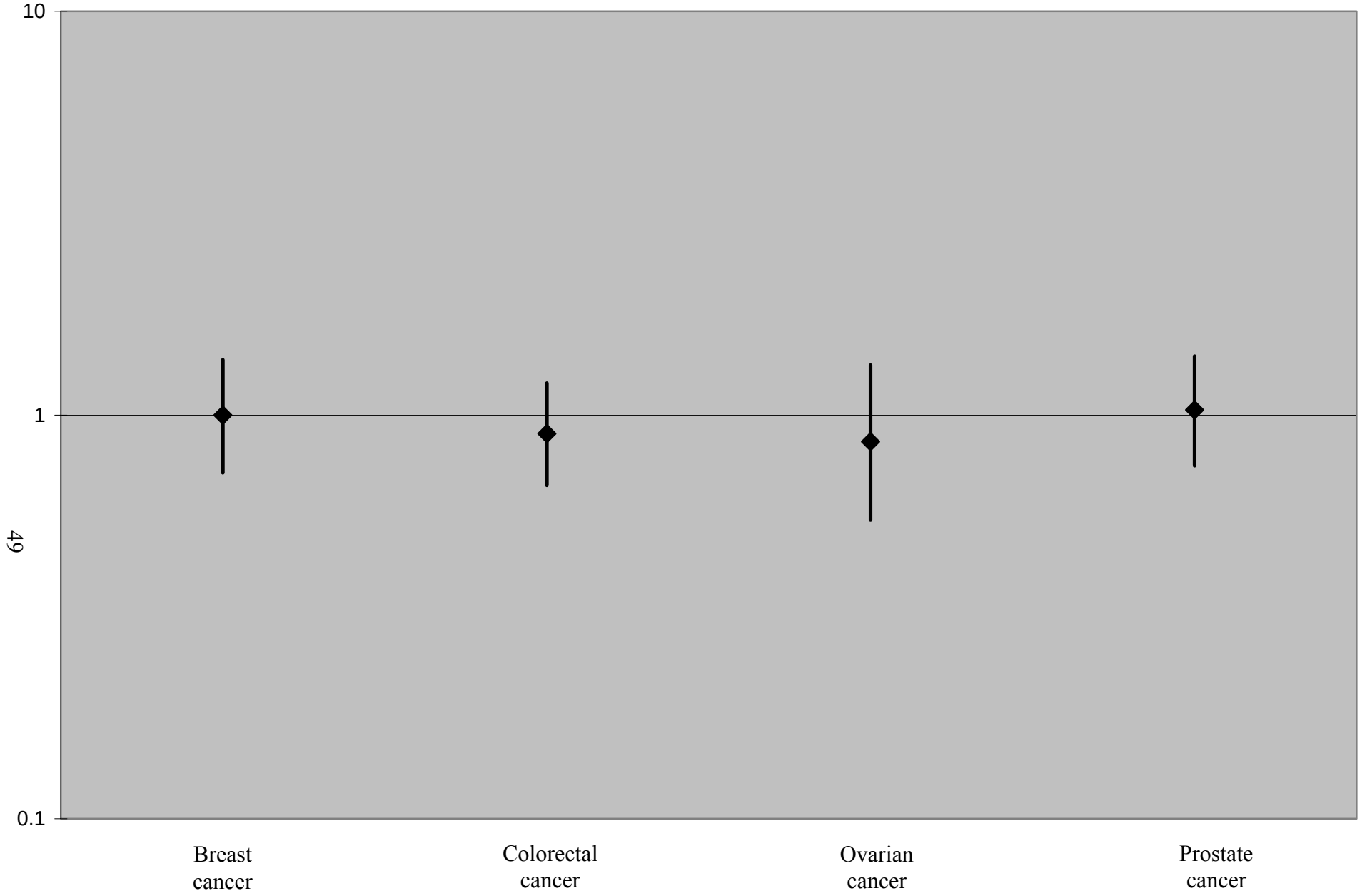


Figure 3.12. Risk of developing cancer for subjects with the highest grouping of DHA intake relative to subjects with the lowest grouping of intake by cancer type.



Aerodigestive Tract Cancer

Overall effect. We identified one study[32] that evaluated the effect of fish consumption on the incidence of upper aerodigestive tract cancer, which was defined as squamous cell carcinoma of the oral cavity/pharynx, esophagus, or larynx. In this study, fish consumption had no significant effect on the incidence of aerodigestive tract cancer. Using fish consumption 1 time per week or less as the referent group, the relative risks of developing aerodigestive tract cancer were 1.02 (0.65-1.61) and 1.37 (0.70-2.69) for men consuming fish 2 to 4 times per week and $\geq$ 5 times per week or more, respectively (Table 3.3).

Sub-populations. The subjects in this one study were from a distinct population, institutionalized American men of Japanese ancestry who resided on the Hawaiian island of Oahu. Analyses of subpopulations were not performed.

Covariates. The effects of covariates on the effect of fish were not assessed.

Effects of dose, source, and exposure duration. Omega-3 dose was not defined in this study. Rather, the amount of fish consumed was described. As noted above, comparisons between different levels of fish consumption and a referent value did not reveal any statistically significant effects. Additionally, with testing across all exposure levels, the p-value for trend was 0.473. Duration of exposure was not defined in this study, and the effects of different durations of exposure were not tested; usual fish intake at baseline between 1965 and 1968 was determined but not assessed subsequently.

Sustainment of Effect. Sustainment of effect was not assessed.

Quality and Applicability. See Table 3.4.

Table 3.3. Risk of upper aerodigestive cancer for different categories of consumption of omega-3 FA, by category.*

Cohort Author, Year	Study arm (quartile, quintile or dose group)	n†	Median intake	Estimates of effect			Multivariate Adjustors
				Age adjusted RR (95% CI)	Multivariate RR (95% CI)		
FISH							
Honolulu Heart Program Chyou, 1995[32]	1	NR	< 1 g/week	NR	1		Age, alcohol, number of cigarettes/day, number of years smoked.
	2	NR	2-4 g/week	NR	1.02	(0.65, 1.61)	
	3	NR	≥ 5 g/week	NR	1.37	(0.70, 2.69)	
	Total 7,995					p = 0.473‡	

* NR = Not Reported; † = Number of people included in analysis; ‡ = test for trend.

Table 3.4. Relationship between methodologic quality and applicability for estimates of effect of omega-3 fatty acid consumption on risk of upper aerodigestive cancer.*

Cohort Author, Year	Applicability	Quality Parameters				
		Adjustment for confounders	Blinding	Valid ascertainment, cases	Valid ascertainment, exposure	Withdrawals and dropouts described
Honolulu Heart Program Chyou, 1995[32]	**III**	**Yes**	**NR**	**Yes**	**Yes**	**Yes**

* NR = Not Reported.

Bladder Cancer

Overall effect. We identified one study[33] that evaluated the effect of fish consumption on the incidence of urinary bladder cancer. In this study, fish consumption had no significant effect on the incidence of bladder cancer. Using fish consumption 1 time per week or less as the referent group, the relative risks of developing bladder cancer were 0.90 (0.59-1.39) and 0.67 (0.26-1.67) for men consuming fish 2 to 4 times per week and 5 times per week or more, respectively (Table 3.5).

Sub-populations. The subjects in this one study were from a distinct population, institutionalized American men of Japanese ancestry who resided on the Hawaiian island of Oahu. Analyses of subpopulations were not performed.

Covariates. The effects of covariates on the effect of fish were not assessed.

Effects of dose, source, and exposure duration. Omega-3 dose was not defined in this study. Rather, the amount of fish consumed was described. As noted above, comparisons between different levels of fish consumption and a referent value did not reveal any statistically significant effects. Additionally, with testing across all exposure levels, the p-value for trend was 0.38. Duration of exposure was not defined in this study, and the effects of different durations of exposure were not tested; usual fish intake at baseline between 1965 and 1968 was determined, but not assessed subsequently.

Sustainment of effect. Sustainment of effect was not assessed.

Quality and applicability. See Table 3.6

Table 3.5. Risk of bladder cancer for different categories of consumption of omega-3 FA, by category.*

Cohort Author, Year	Study arm (quartile, quintile or dose group)	n†	Median intake	Estimates of effect			
				Age adjusted RR (95% CI)	Multivariate RR (95% CI)		Multivariate Adjustors
FISH							
Honolulu Heart Program Chyou, 1993[33]	1	NR	≤ 1 times/week	NR	1		Age, smoking.
	2	NR	2-4 times/week	NR	0.90	(0.59, 1.39)	
	3	NR	≥ 5 times/week	NR	0.67	(0.26, 1.67)	
	Total 7,995					p = 0.377‡	

* NR = Not Reported; † = Number of people included in analysis; ‡ = test for trend.

Table. 3.6. Relationship between methodologic quality and applicability for estimates of effect of omega-3 fatty acid consumption on risk of bladder cancer.*

Cohort Author, Year	Applicability	Quality Parameters				
		Adjustment for confounders	Blinding	Valid ascertainment, cases	Valid ascertainment, exposure	Withdrawals and dropouts described
Honolulu Heart Program Chyou, 1993[33]	**III**	**Yes**	**NR**	**Yes**	**Yes**	**Yes**

* NR = Not Reported.

Breast Cancer

Overall effect. We identified seven studies[37, 41, 43, 44, 51, 52, 55] from six different cohorts that evaluated the effect of omega-3 FA on the incidence of breast cancer. Breast cancer incidence relative to fish consumption was reported in four studies,[41, 43, 52, 55] incidence relative to total and marine omega-3 fatty acid consumption was reported in one,[51] and incidence relative to each of the specific omega-3 FA, DHA, EPA and ALA was reported in one.[37] No significant overall association with the incidence of breast cancer was found with fish, total omega-3 FA, DHA, or EPA consumption (Table 3.7). In one study,[55] women in the highest quartile of fish intake had an increased risk of breast cancer relative to women in the lowest quartile of fish intake (IRR 1.47; 95% CI 1.10, 1.98). Omega-3 FA consumption from marine sources and ALA consumption were associated with a reduced risk of developing breast cancer. Women in the highest quartile of consumption of marine omega-3 FA had a lower incidence of breast cancer than women in the lowest quartile of consumption (RR 0.72, 95% CI 0.53, 0.98). Women in the highest quintile of ALA consumption had a significantly lower incidence of breast cancer than women in the lowest quintile of consumption. This observation held true with adjustment for both age (RR 0.68; 95% CI 0.51, 0.91) and multiple variables (RR 0.70; 95% CI 0.51, 0.97). Associations between ALA consumption and breast cancer incidence were not significant for comparisons between the other quintiles and the lowest quintiles.

Sub-populations. All analyses were restricted to women of racial groups that were homogeneous within, but that differed across, the studies. The four studies that assessed the association between fish consumption and breast cancer incidence used cohorts from the US (Nurses Health Study), Denmark (Diet Cancer and Health Study), and Norway (Norwegian National Health Cohort). The study that assessed the association between the specific omega-3 FA ALA, DHA and EPA used a cohort of women residing in the Netherlands (Netherlands Cohort Study). The study that assessed the association between total omega-3 FA consumption and breast cancer risk used a cohort of Chinese women residing in Singapore (Singapore Chinese Health Study). In this last study, subgroup analyses revealed that the reduced incidence of breast cancer associated with marine omega-3 FA consumption was confined to postmenopausal women and to women with advanced stage disease (stage II or greater). The Nurses Health Study also compared the effect of marine omega-3 FA on premenopausal and postmenopausal women.[44] In this study, a small increased risk of breast cancer was seen among postmenopausal women (RR 1.09; 95% CI 1.02, 1.17), but no significant association was seen overall or for premenopausal women (Table 3.7).

Covariates. The effects of covariates on the effect of omega-3 FA on incidence of breast cancer were assessed in four of the studies. In one study, the risk of developing breast cancer associated with fish intake was not affected by family history of breast cancer, multivitamin use, or glycemic load in separate analyses.[43] In another study, occupational status and BMI did not affect the reported association between fish consumption and breast cancer incidence.[41]

One study examined the relationship between breast cancer incidence, marine omega-3 FA intake, and omega-6 FA intake.[51] In this study, among subjects in the lowest quartile of marine omega-3 FA consumption, breast cancer risk increased significantly with increasing levels of omega-6 FA consumption (p for trend = 0.08). Relative to women in the lowest quartile of both omega-6 and marine omega-3 consumption, the relative risk of developing breast cancer for women in both the lowest quartile of omega-3 consumption and the highest quartile of omega-6 consumption was 1.87 (95% CI, 1.06, 3.27).

One study examined the relationship between fish intake, estrogen receptor (ER) positivity, and cancer incidence. [55] In this study, the incidence rate ratio (IRR) for breast cancer per mean intake of 25 g/d of fish was 1.14 (955 CI 1.03, 1.26) for ER-positive women and 1.00 (95% CI 0.81, 1.24) for ER-negative women.

Effects of dose, source, and exposure duration.

Dose: Each of the studies assessed the effects of dose. No dose effect was observed for fish, total omega-3, DHA, or EPA consumption (Table 3.7). However, dose effects were demonstrated for marine omega-3 FA[51] and ALA[37] (p for trend < 0.05).

Source: No effects were observed for fish in two studies.[41, 43] One study demonstrated a reduced risk for marine omega-3 but not for total omega-3 FA.[51] One study demonstrated reduced risk for ALA but not EPA or DHA.[37] (Table 3.7).

Exposure duration: Three of the studies identified assessed exposure at baseline only; the follow-up period in these studies ranged from 2 to12 years.[37, 41, 51] These studies did not assess the effect of exposure duration. Two cohorts assessed exposure at multiple time points. The Life Span Study[52] and Nurses Health Study[43, 44] collected dietary data at two and four time points, respectively. The Life Span Study found no difference in cancer risk associated with soy products (no association) using dietary data from either dietary survey; this study did not report the effect of exposure duration for fish on the risk of breast cancer. The Nurses Health Study assessed the associations of diet with breast cancer when the diet was assessed only at baseline and also when diet was updated over time without cumulatively averaging in prior intake;[43] results did not change with these analyses.

Sustainment of effect. None of the studies specifically assessed sustainment of effect.

Quality and applicability. See Table 3.8

Table 3.7. Risk of breast cancer for different categories of consumption of omega-3 FA, by category.*

Cohort Author, Year		Study arm (quartile, quintile or dose group)	n†	Median intake	Estimates of effect		
					Age adjusted RR (95% CI)	Multivariate RR (95% CI)	Multivariate Adjustors
FISH							
Diet, Cancer and Health Study Stripp, 2003[55]		1	NR	0-26 g/day	1	1	Age, parity, number of births, age at first birth, BMI, benign breast tumor, years of school, use of HRT, duration of HRT use, alcohol.
		2	NR	27-39 g/day	1.01 (0.77. 1.32)	.99 (0.76, 1.30)	
		3	NR	40-58 g/day	1.17 (0.89, 1.53)	1.12 (0.85, 1.47)	
		4	NR	> 58 g/day	1.54 (1.18, 2.02)	1.47 (1.10, 1.98)	
		Total 23,693					
Nurses' Health Study Holmes, 2003[43]		1	NR	≤ 0.13 servings/day	NR	1	Age, 2yr time period, total energy, alcohol intake, parity and age at first birth, BMI at age 18, weight change since 18, height in inches, family history of breast cancer, history of benign breast disease, age at menarche in years, menopausal status, age at menopausal and HRT use, duration of menopausal.
		2	NR	0.14-0.2 servings/day	NR	.98 (0.89, 1.08)	
		3	NR	0.21-0.27 servings/day	NR	.97 (0.87, 1.08)	
		4	NR	0.28-0.39 servings/day	NR	.99 (0.90, 1.09)	
		5	NR	≥ 0.4 servings/day	NR	1.04 (0.93, 1.14)	
		Total 88,647				p = 0.55‡	
Life Span Study Key, 1999[52]	Fish, not dry	1	NR	≤ 1 times/week	NR	1	Attained age, calendar period, city, age at time of bombing, and radiation dose.
		2	NR	2 - 4 times/week	NR	1.08 (0.84, 1.39)	
		3	NR	≥ 5 times/week	NR	1.17 (0.90, 1.54)	
		4	NR	Unknown	NR	0.92 (0.66, 1.29)	
		Total 34,759				p = 0.21‡	
	Fish, dry	1	NR	≤ 1 times/week	NR	1	
		2	NR	2 - 4 times/week	NR	0.85 (0.64, 1.12)	
		3	NR	≥ 5 times/week	NR	0.49 (0.24, 1.02)	
		4	NR	Unknown	NR	0.77 (0.60, 0.98)	
		Total 34,759				p = 0.03‡	
Norwegian National Health Screening Service Cohort Vatten, 1990[41]		1	NR	≤ 2 g/week	1§	NR	NR
		2	NR	≥ 2 g/week	1.2§ (0.8, 1.7)	NR	
		Total 14,500			p = 0.24‡		

* NR = Not Reported; † = Number of people included in analysis; ‡ = test for trend; § = incidence rate ratio.

Table 3.7 (continued). Risk of breast cancer for different categories of consumption of omega-3 FA, by category.*

Cohort Author, Year	Study arm (quartile, quintile or dose group)	n†	Median intake	Estimates of effect		
				Age adjusted RR (95% CI)	Multivariate RR (95% CI)	Multivariate Adjustors
OMEGA-3						
Singapore Chinese Health Study Gago-Dominguez, 2003[51]	1	NR	NR	NR	1	Age at baseline interview, year of recruitment, dialect group, education, daily alcohol drinker, family history of breast cancer, age when period became regular, number of live births.
	2	NR	NR	NR	0.82 (0.60, 1.1)	
	3	NR	NR	NR	0.84 (0.62, 1.15)	
	4	NR	NR	NR	0.87 (0.64, 1.18)	
	Total 35,298				p = 0.40‡	
ALA						
Netherlands Cohort Study Voorips, 2002[37]	1	NR	0.6	1	1	Age, history of benign breast cancer, breast cancer in one or more sisters, age at menarche, age at menopause, oral contraceptive use, parity, age at first childbirth, Quetelet index, education, alcohol use, current cigarette smoking, total energy intake, total energy-adjusted fat intake.
	2	NR	0.8	0.76 (0.58, 1.00)	0.78 (0.57, 1.05)	
	3	NR	1.0	0.92 (0.71, 1.20)	1.03 (0.76, 1.39)	
	4	NR	1.3	0.69 (0.52, 0.91)	0.74 (0.54, 1.00)	
	5	NR	1.7	0.68 (0.51, 0.91)	0.70 (0.51, 0.97)	
	Total 62,573			p = 0.001‡	p = 0.006‡	

* NR = Not Reported; † = Number of people included in analysis; ‡ = test for trend.

Table 3.7 (continued). Risk of breast cancer for different categories of consumption of omega-3 FA, by category.*

Cohort Author, Year	Study arm (quartile, quintile or dose group)	n†	Median intake	Estimates of effect		
				Age adjusted RR (95% CI)	Multivariate RR (95% CI)	Multivariate Adjustors
EPA						
Netherlands Cohort Study Voorips, 2002[37]	1	NR	0 g/d	1	1	Age, history of benign breast cancer, breast cancer in one or more sisters, age at menarche, age at menopause, oral contraceptive use, parity, age at first childbirth, Quetelet index, education, alcohol use, current cigarette smoking, total energy intake, total energy-adjusted fat intake.
	2	NR	0.01 g/d	1.18 (0.88, 1.56)	1.15 (0.84, 1.58)	
	3	NR	0.02 g/d	1.14 (0.87, 1.50)	1.10 (0.82, 1.49)	
	4	NR	0.04 g/d	1.23 (0.93, 1.62)	1.22 (0.90, 1.65)	
	5	NR	0.08 g/d	1.03 (0.78, 1.37)	0.98 (0.72, 1.35)	
	Total 62,573			p = 0.63‡	p = 0.87‡	
DHA						
Netherlands Cohort Study Voorips, 2002[37]	1	NR	0.01	1	1	Age, history of benign breast cancer, breast cancer in one or more sisters, age at menarche, age at menopause, oral contraceptive use, parity, age at first childbirth, Quetelet index, education, alcohol use, current cigarette smoking, total energy intake, total energy-adjusted fat intake.
	2	NR	0.03	1.11 (0.83, 1.47)	1.10 (0.81, 1.51)	
	3	NR	0.05	1.04 (0.78, 1.37)	1.03 (0.76, 1.40)	
	4	NR	0.08	1.20 (0.91, 1.58)	1.21 (0.90, 1.64)	
	5	NR	0.14	1.02 (0.77, 1.36)	1.00 (0.72, 1.37)	
	Total 62,573			p = 0.62‡	p = 0.70‡	

* NR = Not Reported; † = Number of people included in analysis; ‡ = test for trend.

Table. 3.8 Relationship between methodologic quality and applicability for estimates of effect of omega-3 fatty acid consumption on risk of breast cancer.*

Cohort Author, Year	Applicability	Quality Parameters				
		Adjustment for confounders	Blinding	Valid ascertainment, cases	Valid ascertainment, exposure	Withdrawals and dropouts described
Diet, Cancer and Health Study Stripp[55]	**II**	**Yes**	**NR**	**Yes**	**Yes**	**Yes**
Life Span Study Key, 1999[52]	**III**	**Yes**	**NR**	**Yes**	**Yes**	**Yes**
Netherlands Cohort Study Voorips, 2002[37]	**II**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**
Norwegian National Health Screening Service Cohort Vatten, 1990[41]	**II**	**Yes**	**NR**	**Yes**	**Yes**	**Yes**
Nurses' Health Study Holmes, 2003[43]	**II**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**
Singapore Chinese Health Study Gago-Dominguez, 2003[51]	**II**	**Yes**	**NR**	**Yes**	**Yes**	**No**

* NR = Not Reported.

Colorectal Cancer

Overall effect. We identified six studies[30, 34, 38, 40, 46, 54] from six different cohorts that evaluated the effect of omega-3 FA on the incidence of colorectal cancer. Colorectal cancer incidence relative to fish consumption was reported in four studies,[30, 38, 40, 46] incidence relative to total omega-3 fatty acid consumption was reported in one,[34] and incidence relative to each of the specific omega-3 FA, DHA, EPA and ALA was reported in one.[54] Among the studies that measured fish consumption, three found no association with the incidence of colorectal cancer;[30, 38, 46] one study[40] demonstrated a reduced risk among subjects in the highest quartile of fish intake relative to subjects in the lowest quartile of fish intake (RR 0.49, 95% CI 0.27, 0.89). The one study that measured total omega-3 FA consumption[34] demonstrated a trend for reducing the risk of colorectal cancer with higher consumption of omega-3 FA when adjusting only for age. However, with adjustment for multiple variables no significant association was observed between omega-3 fatty acid consumption and the incidence of colorectal cancer. No significant association with the incidence of colorectal cancer was found with ALA, DHA, or EPA consumption[54] (Table 3.9).

Sub-populations. Three of the studies were among cohorts of women,[34, 40, 46] one among a cohort of men,[30] and two among cohorts that included both men and women.[38, 54] Among the latter, one study performed subgroup analyses among men and women and found no association between fish consumption and colon cancer for men or women.[38] The one study that demonstrated a favorable association between a source of omega-3 FA and incidence of colorectal cancer after adjustment for multiple variables was performed in a cohort of women.[40]

Three of the studies assessed the incidence of colon cancer only[34, 38, 46] and three assessed the incidence of colorectal cancer including cancers of the colon or rectum.[30, 40, 54] In the one study that assessed the incidence of colon cancer, rectal cancer, and colorectal cancer,[54] there was no difference in the association between ALA, EPA, or DHA intake and the incidence of any of these types of cancer, i.e., there was no association in any case. The one study that demonstrated a favorable association between a source of omega-3 FA and incidence of colorectal cancer after adjustment for multiple variables included both cancers of the colon and rectum to define colorectal cancer.[40]

Covariates. Although each of the studies performed multivariable analyses, the effects of specific covariates were not reported.

Effects of dose, source, and exposure duration.

Dose: Each of the studies assessed the effects of dose. The one study[40] that demonstrated a reduced risk of colorectal cancer among subjects in the highest quartile of fish intake relative to subjects in the lowest quartile of fish intake also reported a significant test for trend across all quartiles ($p = 0.007$). However, comparisons of cancer incidence between the first quartile and each of the second and third quartiles of fish intake did not yield significant results. One additional study[34] demonstrated a trend for reducing the risk of colorectal cancer with higher consumption of omega-3 FA, when adjusting only for age. However, there was no significant dose effect with adjustment for multiple variables. None of the other studies demonstrated a dose effect.[30, 38, 46, 54]

Source: One study demonstrated a reduced risk for fish;[40] three did not.[30, 38, 46] One study demonstrated a reduced risk for omega-3 FA consumption that was not significant after adjustment for multiple variables.[34] One study assessed the effects of different types of omega-3 FA on the incidence of colorectal cancer and found no association with ALA, DHA, or EPA consumption.[54]

Exposure duration: Four of the studies assessed exposure at baseline only,[34, 38, 40, 54] and two assessed exposure at multiple time points. However, none specifically assessed the effect of exposure duration on the incidence of colorectal cancer.

Sustainment of Effect. None of the studies specifically assessed sustainment of effect.

Quality and applicability. See Table 3.10

Table 3.9. Risk of colorectal cancer for different categories of consumption of omega-3 FA, by category.*

Cohort Author, Year	Study arm (quartile, quintile or dose group)	n†	Median intake	Estimates of effect		
				Age adjusted RR (95% CI)	Multivariate RR (95% CI)	Multivariate Adjustors
FISH						
Health Professionals Follow-up Study Giovannucci, 1994[30]	1	NR	8.4 g/d	1	NR	NR
	2	NR	20.9 g/d	0.85 (0.54, 1.33)	NR	
	3	NR	31.0 g/d	1.05 (0.68, 1.61)	NR	
	4	NR	47.8 g/d	0.80 (0.51, 1.26)	NR	
	5	NR	83.4 g/d	1.06 (0.70, 1.60)	NR	
	Total 47,949		p = 0.79‡			
Netherlands Cohort Study Goldbohm, 1994[38]	1	NR	0 g/d	NR	1	Age and energy.
	2	NR	0-10 g/d	NR	1 (0.68, 1.47)	
	3	NR	10-20 g/d	NR	0.74 (0.48, 1.15)	
	4	NR	> 20 g/d	NR	0.81 (0.56, 1.17)	
	Total 3,111				p = 0.14‡	
Nurses' Health Study Willett, 1990[46]	1	NR	< 1 g/month	1	NR	NR
	2	NR	1-3 g/month	1.29 (0.70, 2.40)	NR	
	3	NR	1 g/week	0.92 (0.49, 1.72)	NR	
	4	NR	2-4 g/week	0.75 (0.35, 1.58)	NR	
	5	NR	4 g/week	1.06 (0.36, 3.12)	NR	
	Total 88,751		p = 0.09‡			

* NR = Not Reported; † Number of people included in analysis; ‡ = test for trend.

Table 3.9 (continued). Risk of colorectal cancer for different categories of consumption of omega-3 FA, by category.*

Cohort Author, Year		Study arm (quartile, quintile or dose group)	n†	Median intake	Estimates of effect			Multivariate Adjustors
					Age adjusted RR (95% CI)	Multivariate RR (95% CI)		
FISH								
New York University Women's Health Study Kato, 1997[40]		1	NR	NR	NR	1		Age, total calorie, place at enrollment and highest level of education.
		2	NR	NR	NR	1.01	(0.62, 1.67)	
		3	NR	NR	NR	0.65	(0.37, 1.13)	
		4	NR	NR	NR	0.49	(0.27, 0.89)	
		Total 14,727					p = 0.007‡	
Omega-3								
Iowa Women's Health Study Bostick, 1994[34]		1	NR	< 0.03 g/day	1	1		Age, total energy intake, height, parity, total vitamin E, a total vitamin E by age interaction term, vitamin A supplement intake.
		2	NR	0.03-0.05 g/day	0.67 NR	0.82	(0.55, 1.24)	
		3	NR	0.06-0.10 g/day	0.61 NR	0.77	(0.50, 1.17)	
		4	NR	0.11-0.18 g/day	0.72 NR	0.96	(0.64, 1.43)	
		5	NR	> 0.18 g/day	0.60 NR	0.70	(0.45, 1.09)	
		Total 35,215			p = 0.04‡		p = 0.26‡	
ALA								
Swedish women in mammography-screening program Terry, 2001[54]	Colorectal	1	NR	0.45 g/d	NR	1		Age, BMI, education level, energy intake, intakes of red meat and alcohol, energy, dietary fiber, calcium, vitamin C, folic acid, Vitamin D, saturated fat, monounsaturated fat, polyunsaturated fat.
		2	NR	0.50 g/d	NR	0.96	(0.73, 1.27)	
		3	NR	0.54 g/d	NR	0.96	(0.72, 1.28)	
		4	NR	0.70 g/d	NR	0.99	(0.75, 1.32)	
		Total 61,463					p = 0.99‡	
	Colon	1	NR	0.45 g/d	NR	1		
		2	NR	0.50 g/d	NR	0.96	(0.68, 1.35)	
		3	NR	0.54 g/d	NR	0.96	(0.67, 1.3)	
		4	NR	0.70 g/d	NR	0.90	(0.63, 1.28)	
		Total 61,463					p = 0.57‡	
	Rectal	1	NR	0.45 g/d	NR	1		
		2	NR	0.50 g/d	NR	0.95	(0.60, 1.52)	
		3	NR	0.54 g/d	NR	0.92	(0.56, 1.49)	
		4	NR	0.70 g/d	NR	1.11	(0.70, 1.78)	
		Total 61,463						

* NR = Not Reported; † Number of people included in analysis; ‡ = test for trend.

Table 3.9 (continued). Risk of colorectal cancer for different categories of consumption of omega-3 FA, by category.*

Cohort Author, Year		Study arm (quartile, quintile or dose group)	n†	Median intake	Estimates of effect			Multivariate Adjustors
					Age adjusted RR (95% CI)	Multivariate RR (95% CI)		
EPA								
Swedish women in mammography-screening program Terry, 2001[54]	Colorectal	1	NR	0.03 g/d	NR	1		Age, BMI, education level, energy intake, intakes of red meat and alcohol, energy, dietary fiber, calcium, vitamin C, folic acid, Vitamin D, saturated fat, monounsaturated fat, polyunsaturated fat.
		2	NR	0.05 g/d	NR	0.80	(0.68, 1.15)	
		3	NR	0.07 g/d	NR	0.96	(0.73, 1.26)	
		4	NR	0.09 g/d	NR	0.96	(0.72, 1.28)	
		Total 61,463					p = 0.91‡	
	Colon	1	NR	0.03 g/d	NR	1		
		2	NR	0.05 g/d	NR	0.76	(0.54, 1.06)	
		3	NR	0.07 g/d	NR	0.81	(0.58, 1.15)	
		4	NR	0.09 g/d	NR	0.85	(0.60, 1.21)	
		Total 61,463					p = 0.46‡	
	Rectal	1	NR	0.03 g/d	NR	1		
		2	NR	0.05 g/d	NR	1.17	(0.75, 1.83)	
		3	NR	0.07 g/d	NR	1.29	(0.80, 2.06)	
		4	NR	0.09 g/d	NR	1.25	(0.75, 2.06)	
		Total 61,463					p = 0.35‡	
DHA								
Swedish women in mammography-screening program Terry, 2001[54]	Colorectal	1	NR	0.08 g/d	NR	1		Age, BMI, education level, energy intake, intakes of red meat and alcohol, energy, dietary fiber, calcium, vitamin C, folic acid, Vitamin D, saturated fat, monounsaturated fat, polyunsaturated fat.
		2	NR	0.11 g/d	NR	0.88	(0.67, 1.15)	
		3	NR	0.13 g/d	NR	0.87	(0.66, 1.15)	
		4	NR	0.18 g/d	NR	0.90	(0.67, 1.20)	
		Total 61,463					p = 0.52‡	
	Colon	1	NR	0.08 g/d	NR	1		
		2	NR	0.11 g/d	NR	0.84	(0.60, 1.17)	
		3	NR	0.13 g/d	NR	0.74	(0.51, 1.06)	
		4	NR	0.18 g/d	NR	0.88	(0.61, 1.26)	
		Total 61,463					p = 0.41‡	
	Rectal	1	NR	0.08 g/d	NR	1		
		2	NR	0.11 g/d	NR	1.03	(0.66, 1.61)	
		3	NR	0.13 g/d	NR	1.16	(0.73, 1.8)	
		4	NR	0.18 g/d	NR	1.03	(0.62, 1.71)	
		Total 61,463					p = 0.79‡	

* NR = Not Reported; † Number of people included in analysis; ‡ = test for trend.

Table 3.10. Relationship between methodologic quality and applicability for estimates of effect of omega-3 fatty acid consumption on risk of colorectal cancer.*

Cohort Author, Year	Applicability	Quality Parameters				
		Adjustment for confounders	Blinding	Valid ascertainment, cases	Valid ascertainment, exposure	Withdrawals and dropouts described
Health Professionals Follow-up Study Giovannucci, 1994[30]	II	Yes	Yes	Yes	Yes	Yes
Netherlands Cohort Study Goldbohm, 1994[38]	II	Yes	NR	Yes	Yes	No
Nurses' Health Study Willett, 1990[46]	II	Yes	Yes	Yes	Yes	Yes
New York University Women's Health Study Kato, 1997[40]	III	Yes	NR	Yes	Yes	Yes
Iowa Women's Health Study Bostick, 1994[34]	II	Yes	NR	Yes	Yes	Yes
Swedish women in mammography-screening program Terry, 2001[54]	II	Yes	No	Yes	Yes	NR

* NR = Not Reported.

Lung Cancer

Overall effect. We identified three studies[24, 42, 56] from three different cohorts that evaluated the effect of omega-3 FA on the incidence of lung cancer and one that evaluated the effect of omega-3 FA intake on death from lung cancer.[36] All of these studies assessed lung cancer incidence relative to fish consumption (Table 3.11). In one study,[24] fish consumption was associated with a reduced risk of lung cancer (RR 0.32, 95% CI 0.13, 0.76). In the other studies, no significant association was found between fish intake and lung cancer incidence[42, 56] or death from lung cancer.[36]

Sub-populations. Each of the cohorts was population-based and included men and women. The base population comprised residents of a single rural prefecture in Japan in one study,[24] 19 Japanese prefectures in another study,[36] and people residing in Norway in the other two.[42, 56] One study reported the risk of dying from lung cancer stratified by gender.[36] This study found no significant association between fish consumption and death from lung cancer for either men or women (Table 3.11).

Covariates. The effects of different methods of cooking fish on the incidence of lung cancer were assessed in one study.[24] Consumption of fish that had been broiled or boiled was associated with reduced risk for lung cancer (p values for trend < 0.02). No significant reduction in risk of lung cancer was found for consumption of fish that was raw or deep-fried.

Effects of dose, source, and exposure duration.

Dose: Three of the studies assessed the effects of dose.[24, 36, 42] The study that reported a reduced risk of lung cancer with fish consumption, also reported a dose effect.[24] Subjects in each the middle and high consumption categories had a lower risk relative to subjects in the lowest category of consumption and the risk decreased with higher consumption (p for trend = 0.003). No overall or dose effect was observed in the other studies.[24, 42]

Source: The source of omega-3 fatty acid was fish in each of the studies.

Exposure duration: Each of the studies assessed fish consumption at baseline only; the follow-up period in these studies ranged from 8 to14 years. None of the studies assessed the effect of exposure duration.

Sustainment of effect. Neither of the studies specifically assessed sustainment of effect.

Quality and applicability. See Table 3.12.

Table 3.11. Risk of lung cancer for different categories of consumption of omega-3 FA, by category.*

Cohort Author, Year		Study arm (quartile, quintile or dose group)	n†	Median intake	Estimates of effect			
					Age adjusted RR (95% CI)	Multivariate RR (95% CI)		Multivariate Adjustors
FISH								
Aichi Prefecture Cohort, Japan Takezaki, 2003[24]		1	174	< 1 times/week	NR	1		Age, sex, smoke, occupation.
		2	1,264	1-2 times/week	NR	0.99	(0.48, 2.03)	
		3	1,360	≥ 3 times/week	NR	0.32	(0.13, 0.76)	
		Total 5,885					p = 0.003‡	
Japan Collaborative Cohort Ozasa, 2001[36]	Men	1	NR	≤ 1-2 times/week	NR	1§		Age, parent's history of lung cancer, smoking status, smoking index and time since quitting smoking.
		2	NR	3-4 times/week	NR	1.12§	(0.87, 1.43)	
		3	NR	almost every day	NR	1.03§	(0.79, 1.34)	
		Total 42,940					p = 0.72‡	
	Women	1	NR	≤ 1-2 times/week	NR	1		
		2	NR	3-4 times/week	NR	0.73	(0.45, 1.21)	
		3	NR	almost every day	NR	0.88	(0.52, 1.49)	
		Total 55,308					p = 0.50‡	
Norwegian Cohorts Kvale, 1983[56]	Histologic verification	1	NR	< 10 times/month	NR	1		Age, cigarette smoking, region and urban/rural place of residence.
		2	NR	10-14 times/month	NR	NR		
		3	NR	15-19 times/month	NR	NR		
		4	NR	≥ 20 times/month	NR	0.82	NR	
		Total 13785					p = 0.63‡	
	Squamous and small-cell carcinomas	1	NR	< 10 times/month	NR	1		
		2	NR	10-14 times/month	NR	NR		
		3	NR	15-19 times/month	NR	NR		
		4	NR	≥ 20 times/month	NR	0.98	NR	
		Total 13785					p = 0.99‡	
Norwegian National Health Screening Service Cohort Veierod, 1997[42]		1	NR	<1 times/week		1§		Smoking status, gender, age at inclusion, attained age.
		2	NR	1-2 times/week		1.1‖	(0.6, 2.2)	
		3	NR	3-4 times/week		1.0‖	(0.5, 2.1)	
		4	NR	≥ 5 times/week		3.0‖	(1.2, 7.3)	
		Total 51,452					p = 0.2‡	

* NR = Not Reported; † Number of people included in analysis; ‡ = test for trend; § Hazard Ratio; || Incidence Rate Ratio.

Table 3.12. Relationship between methodologic quality and applicability for estimates of omega-3 fatty acid consumption on risk of lung cancer.*

Cohort Author, Year	Applicability	Quality Parameters				
		Adjustment for confounders	Blinding	Valid ascertainment, cases	Valid ascertainment, exposure	Withdrawals and dropouts described
Aichi Prefecture Cohort, Japan Takezaki, 2003[24]	II	Yes	NR	Yes	Yes	NR
Japan Collaborative Cohort Ozasa, 2001[36]	II	Yes	NR	Yes	Yes	Yes
Norwegian Cohorts Kvale, 1983[56]	II	Yes	NR	Yes	Yes	Yes
Norwegian National Health Screening Service Cohort Veierod, 1997[42]	II	Yes	NR	Yes	Yes	Yes

* NR = Not Reported.

Lymphoma

Overall effect. We identified two studies from two different cohorts that evaluated the effect of omega-3 FA on the incidence of non-Hodgkin's lymphoma.[35, 47] One study assessed incidence relative to fish consumption, the other relative to marine omega-3 fat consumption. Neither study found a significant association between fish intake and the incidence of non-Hodgkin's lymphoma (Table 3.13).

Sub-populations. Both cohorts were restricted to women. The Nurses Health Study cohort includes U.S. female registered nurses who responded to a mailed questionnaire.[47] The Iowa Women's Health Study cohort includes women who had valid Iowa driver's licenses at the time of recruitment. Analyses on subpopulations were not reported in either study.

Covariates. The effects of covariates on risk associated with omega-3 FA were not reported.

Effects of dose, source, and exposure duration.

Dose: Both studies assessed the risk of developing non-Hodgkin's lymphoma given different levels of fish or omega-3 fat consumption and found no dose effect (p for trend > 0.40 for all comparisons).

Source: The source of omega-3 fatty acid was fish in one study[35] and marine omega-3 FA in the other.[47]

Exposure duration: Each of the studies assessed fish consumption at baseline only; the follow-up period in these studies ranged from 6 to14 years. Neither study assessed the effect of exposure duration to omega-3 FA on risk of non-Hodgkin's lymphoma.

Sustainment of effect. Neither of the studies specifically assessed sustainment of effect.

Quality and applicability. See Table 3.14.

Table 3.13. Risk of non-hodgkin's lymphoma for different categories of consumption of omega-3 FA, by category.*

Cohort Author, Year	Study arm (quartile, quintile or dose group)	n†	Median intake	Estimates of effect		Multivariate Adjustors
				Age adjusted RR (95% CI)	Multivariate RR (95% CI)	
FISH						
Iowa Women's Health Study Chiu, 1996[35]	1	NR	< 4 servings/ month	NR	1	Age and energy.
	2	NR	4-6 servings/ month	NR	0.94 (0.59, 1.49)	
	3	NR	> 6 servings/ month	NR	0.81 (0.49, 1.35)	
	Total 35,156				p = 0.42‡	
Omega-3						
Nurses' Health Study Zhang, 1999[47]	1	NR	0.02 % of energy intake	1	1	Age, total energy, length of follow-up, geographic region, cigarette smoke, height in inches, saturated and trans unsaturated fats, fruit, vegetable intake.
	2	NR	0.03 % of energy intake	1.2 NR	1.2 NR	
	3	NR	0.04 % of energy intake	1.3 NR	1.4 NR	
	4	NR	0.05 % of energy intake	1.1 NR	1.2 NR	
	5	NR	0.10 % of energy intake	1.1 (0.7, 1.7)	1.4 (0.8, 2.2)	
	Total 88,410			p = 0.90‡	Testing NR	

* NR = Not Reported; † Number of people included in analysis; ‡ = test for trend.

Table 3.14. Relationship between methodologic quality and applicability for estimates of effect of omega-3 fatty acid consumption on risk of non-Hodgkin's lymphoma.*

Cohort Author, Year	Applicability	Quality Parameters				
		Adjustment for confounders	Blinding	Valid ascertainment, cases	Valid ascertainment, exposure	Withdrawals and dropouts described
Iowa Women's Health Study Chiu, 1996[35]	II	Yes	NR	Yes	Yes	Yes
Nurses' Health Study Zhang, 1999[47]	II	Yes	Yes	Yes	Yes	Yes

* NR = Not Reported.

Ovarian Cancer

Overall Effect. We identified one report[48] that evaluated the effect of different kinds of fat, including the omega-3 FA DHA, EPA, and ALA, on the incidence of ovarian cancer among women enrolled in the Nurses Health Study. This study found no evidence of an association between intake of any type of fat, including DHA, EPA, and ALA, and the incidence of ovarian cancer (Table 3.15). Secondary analyses showed that total fat intake (i.e., different levels of total fat intake) had no effect on the development of specific subtypes of ovarian cancer (serous, mucinous, and endometrial tumors). However, these analyses were not conducted for omega-3 FA specifically.

Sub-populations. The subjects in this study were all female registered nurses in the US. The effect of total fat intake, but not omega-3 FA intake was assessed for several different subpopulations. The relation between fat intake and ovarian cancer risk (i.e., no association) did not differ substantially by age or menopausal status.

Covariates. The effects of several covariates on the effect of total fat intake but not omega-3 fat were assessed. Neither body mass index, oral contraceptive use, smoking status, nor physical activity level had an effect on the relation between fat intake and ovarian cancer.

Effects of dose, source, and exposure duration.

Dose: No dose effect was observed for ALA, DHA, or EPA consumption (Table 3.15).

Source: The effects of source were not specifically assessed.

Exposure duration: This study assessed dietary intake at four time points. Analyses that excluded cases diagnoses during the first 2 and 4 years of follow-up did not differ in their findings from analyses including all cases.

Sustainment of effect. Sustainment of effect was not assessed.

Quality and applicability. See Table 3.16.

Table. 3.15. Risk of ovarian cancer for different categories of consumption of omega-3 FA, by category.*

Cohort Author, Year	Study arm (quartile, quintile or dose group)	n†	Median intake	Estimates of effect		Multivariate Adjustors
				Age adjusted RR (95% CI)	Multivariate RR (95% CI)	
ALA						
Nurses' Health Study Bertone, 2002[48]	1	NR	NR	1.0	1.0	Age, parity, age at menarche, oral contraceptive use and duration, menopausal status/postmenopausal hormone use, smoking status.
	2	NR	NR	0.74 NR	0.95 (0.68, 1.33)	
	3	NR	NR	0.62 NR	0.80 (0.56, 1.14)	
	4	NR	NR	0.86 NR	0.82 (0.58, 1.15)	
	5	NR	NR	0.98 NR	0.88 (0.62, 1.24)	
	Total 80,258				p = 0.27‡	
EPA						
Nurses' Health Study Bertone, 2002[48]	1	NR	NR	1	1	Age, parity, age at menarche, oral contraceptive use and duration, menopausal status/postmenopausal hormone use, smoking status.
	2	NR	NR	1.01 NR	1.04 (0.68, 1.59)	
	3	NR	NR	0.73 NR	0.75 (0.47, 1.17)	
	4	NR	NR	0.96 NR	1.00 (0.66, 1.52)	
	5	NR	NR	0.96 NR	0.97 (0.64, 1.48)	
	Total 80,258				p = 0.80‡	
DHA						
Nurses' Health Study Bertone, 2002[48]	1	NR	NR	1	1	Age, parity, age at menarche, oral contraceptive use and duration, menopausal status/postmenopausal hormone use, smoking status.
	2	NR	NR	1.06 NR	1.06 (0.70, 1.61)	
	3	NR	NR	0.67 NR	0.67 (0.42, 1.08)	
	4	NR	NR	1.05 NR	1.07 (0.71, 1.63)	
	5	NR	NR	0.88 NR	0.86 (0.55, 1.33)	
	Total 80,258				p = 0.52‡	

* NR = Not Reported; † Number of people included in analysis; ‡ = test for trend.

Table 3.16. Relationship between methodologic quality and applicability for estimates of effect of omega-3 fatty acid consumption on risk of ovarian cancer.

Cohort Author, Year	Applicability	Quality Parameters				
		Adjustment for confounders	Blinding	Valid ascertainment, cases	Valid ascertainment, exposure	Withdrawals and dropouts described
Nurses' Health Study Bertone, 2002[48]	II	Yes	Yes	Yes	Yes	Yes

Pancreatic Cancer

Overall Effect. We identified two studies[25, 49] from two different cohorts that evaluated the effect of omega-3 FA on the incidence of pancreatic cancer. One study assessed incidence relative to fish, omega-3 FA, and ALA consumption;[25] the other assessed incidence relative to ALA consumption.[49] There was no significant association between fish intake and any of these measures of omega-3 FA in either study (Table 3.17).

Sub-populations. One cohort comprised women, the other men. The Nurses Health Study cohort includes U.S. female registered nurses who responded to a mailed questionnaire.[49] The Alpha-tocopherol, Beta-Carotene Cancer Prevention Study cohort includes male smokers. Analyses of the relationship between omega-3 FA and pancreatic cancer risk for subpopulations were not reported in either study.

Covariates. The effects of covariates on risk associated with omega-3 FA were not reported.

Effects of dose, source, and exposure duration.

Dose: Both studies assessed the risk of developing pancreatic cancer given different levels of fish or omega-3 FA consumption and found no dose effect (p for trend > 0.10 for all comparisons).

Source: One study assessed incidence relative to fish, omega-3 FA and ALA consumption;[25] the other assessed incidence relative to ALA consumption.[49]

Exposure duration: One study assessed fish consumption at baseline only.[25] The other study[49] assessed dietary intake at four time points but did not report the effect of the duration of exposure to omega-3 FA and pancreatic cancer.

Sustainment of effect. Neither of the studies specifically assessed sustainment of effect.

Quality and applicability. See Table 3.18.

Table 3.17. Risk of pancreatic cancer for different categories of consumption of omega-3 FA, by category.*

Cohort Author, Year	Study arm (quartile, quintile or dose group)	n†	Median intake	Estimates of effect			Multivariate Adjustors
				Age adjusted RR (95% CI)	Multivariate RR (95% CI)		
Fish							
Alpha-tocopherol, Beta-Carotene Cancer Prevention Study Stolzenberg-Solomon, 2002[25]	1	NR	NR	NR	1		Energy intake by the residual method, age, and years of smoking, energy-adjusted saturated fat intake.
	2	NR	NR	NR	1.22	(0.75, 1.97)	
	3	NR	NR	NR	1.14	(0.70, 1.86)	
	4	NR	NR	NR	1.07	(0.65, 1.76)	
	5	NR	NR	NR	0.91	(0.54, 1.52)	
	Total 27,111					p = 0.59‡	
Omega-3							
Alpha-tocopherol, Beta-Carotene Cancer Prevention Study Stolzenberg-Solomon, 2002[25]	1	NR	NR	NR	1		Energy intake by the residual method, age, and years of smoking.
	2	NR	NR	NR	0.97	(0.60, 1.60)	
	3	NR	NR	NR	1.04	(0.64, 1.69)	
	4	NR	NR	NR	1.16	(0.72, 1.86)	
	5	NR	NR	NR	0.96	(0.58, 1.58)	
	Total 27,111					p = 0.90‡	
ALA							
Nurses' Health Study Michaud, 2003[49]	1	NR	0.7 g/d	1	1		Pack-years of smoking, BMI, history of diabetes mellitus, caloric intake, height, physical activity, menopausal status, glycemic load intake.
	2	NR	0.8 g/d	1.03	1.08	(0.70, 1.67)	
	3	NR	0.9 g/d	1	1.03	(0.66, 1.61)	
	4	NR	1.0 g/d	0.75	0.80	(0.49, 1.30)	
	5	NR	1.1 g/d	0.76	0.77	(0.47, 1.26)	
	Total 88,802			p = 0.12‡		p = 0.16‡	
Alpha-tocopherol, Beta-Carotene Cancer Prevention Study Stolzenberg-Solomon, 2002[25]	1	NR	NR	NR	1		Energy intake by the residual method, age, and years of smoking, energy-adjusted saturated fat intake.
	2	NR	NR	NR	1.09	(0.69, 1.73)	
	3	NR	NR	NR	1.10	(0.68, 1.79)	
	4	NR	NR	NR	1.04	(0.61, 1.77)	
	5	NR	NR	NR	1.11	(0.65, 1.91)	
	Total 27,111					p = 0.77‡	

* NR = Not Reported; † Number of people included in analysis; ‡ = test for trend.

Table 3.18. Relationship between methodologic quality and applicability for estimates of effect of omega-3 fatty acid consumption on risk of pancreatic cancer.*

Cohort Author, Year	Applicability	Quality Parameters				
		Adjustment for confounders	Blinding	Valid ascertainment, cases	Valid ascertainment, exposure	Withdrawals and dropouts described
Alpha-tocopherol, Beta-Carotene Cancer Prevention Study Stolzenberg-Solomon, 2002[25]	III	Yes	NR	Yes	Yes	Yes
Nurses' Health Study Michaud, 2003[49]	II	Yes	Yes	Yes	Yes	Yes

* NR = Not Reported.

Prostate Cancer

Overall effect. We identified seven studies[27-29, 39, 50, 53, 57] from five different cohorts that evaluated the effect of omega-3 FA on the incidence of prostate cancer. Prostate cancer incidence relative to fish consumption was reported in four studies,[27, 28, 50, 53] relative to marine omega-3 fatty acid consumption in one,[29] relative to the specific omega-3 FA DHA and EPA in two, [39, 57] and relative to the specific omega-3 fatty acid ALA in three.[29, 39, 57] Among the four studies that assessed risk relative to fish consumption, one demonstrated a favorable effect[53] and one an unfavorable effect.[50] For ALA, there was no association with overall prostate cancer risk in two studies.[29, 39, 57] However, one of these studies demonstrated increased risk for advanced prostate cancer;[57] the other did not.[39] No significant association with the incidence of prostate cancer was found with marine omega-3 fats, DHA, or EPA consumption (Table 3.19).

Sub-populations. All analyses were restricted to men of racial groups that were homogeneous within, but that differed across, the studies. These studies followed cohorts that are ethnically, geographically, and/or socio-economically distinct. The base populations for these studies comprised Hawaiian men of Japanese ancestry,[27] Seventh Day Adventist men residing in California,[50] US male health professionals,[28, 60] Swedish male twin pairs,[53] and the Dutch population.[39] These studies did not perform analyses of specific subpopulations.

Covariates. The effects of covariates on the effect of omega-3 on incidence of prostate cancer were not assessed in these studies.

Effects of dose, source, and exposure duration.

Dose and source: Each of the studies assessed the effects of dose. Dose effects in opposite directions for fish consumption were reported for two studies;[50, 53] no dose effect for fish was found in two.[27, 28] Dose effects in opposite directions for ALA consumption were reported by two studies.[29, 39] One of these studies[29] found an inverse dose effect for overall prostate cancer risk and proportionate dose effect for advanced prostate cancer, although the inverse dose effect for overall prostate cancer risk did not persist with multivariable adjustment. No dose effect was reported for marine omega-3 FA,[29] DHA, or EPA[39] (Table 3.19).

Exposure duration: Four of the cohorts identified assessed exposure at baseline only; the follow-up period in these studies ranged from 6 to30 years.[27, 39, 50, 53] These studies did not assess the effect of exposure duration. One cohort assessed exposure at multiple time points. The Health Professionals Follow-up Study[28, 29, 57] collected dietary data at three time points but did not report the effect of exposure duration on the risk of prostate cancer.

Sustainment of effect. None of the studies specifically assessed sustainment of effect.

Quality and applicability. See Table 3.20.

Table 3.19. Risk of prostate cancer for different categories of consumption of omega-3 FA, by category.*

Cohort Author, Year	Study arm (quartile, quintile or dose group)	n†	Median intake	Estimates of effect				
				Age adjusted RR (95% CI)		Multivariate RR (95% CI)		Multivariate Adjustors
Fish								
Hawaii Health Surveillance Program LeMarchand, 1994[27]	1	NR	NR	NR		1		Age, race, income.
	2	NR	NR	NR		1.1	(0.7, 1.7)	
	3	NR	NR	NR		0.9	(0.6, 1.3)	
	4	NR	NR	NR		1.2	(0.8, 1.8)	
	Total 8,881						p = 0.55‡	
Health Professionals Follow-up Study Augustsson, 2003[28]	1	NR	< 2 times/month	1		1		Age, calories, fatty acid, lycopene, retinol, vitamin D and physical activity.
	2	NR	2 times/month-1 time/week	1.06	(0.92, 1.22)	1.05	(0.91, 1.21)	
	3	NR	2-3 times/week	1.06	(0.94, 1.20)	1.06	(0.93, 1.20)	
	4	NR	> 3 times/week	0.91	(0.79, 1.05)	0.93	(0.80, 1.08)	
	Total 47,882							
Seventh-day Adventist Mills, 1989[50]	1	NR	Never	1		NR		NR
	2	NR	< 1 g/week	1.68	(1.16, 2.43)	NR		
	3	NR	≥ 1 g/week	1.47	(0.84, 2.60)	NR		
	Total 14,000			p = 0.03‡				
Swedish Twin Registry Terry, 2001[53]	1	NR	Never/ seldom	1.7	(1.0, 3.0)	2.3	(1.2, 4.5)	Age, BMI, physical activity, smoking, consumption of alcohol, red meat, processed meat, fruit, vegetable and milk.
	2	NR	Small	1.1	(0.9, 1.3)	1.2	(1.0, 1.4)	
	3	NR	Moderate	1		1		
	4	NR	Large	1.1	(0.8, 1.5)	1.0	(0.7, 1.6)	
	Total 6,272			p = 0.35‡		p = 0.05‡		
Marine Omega-3								
Health Professionals Follow-up Study Giovannucci, 1993[29]	1	NR	0.05 g/d	1		NR		NR
	2	NR	0.12 g/d	1.34	(0.78, 2.30)	NR		
	3	NR	0.21 g/d	1.05	(0.59, 1.89)	NR		
	4	NR	0.30 g/d	0.92	(0.51, 1.65)	NR		
	5	NR	0.55 g/d	0.90	(0.51, 1.61)	NR		
	Total 47,855		p = 0.30‡					

* NR = Not Reported; † Number of people included in analysis; ‡ = test for trend.

Table 3.19 (continued). Risk of prostate cancer for different categories of consumption of omega-3 FA, by category.*

Cohort Author, Year	Study arm (quartile, quintile or dose group)	n†	Median intake	Estimates of effect		Multivariate Adjustors
				Age adjusted RR (95% CI)	Multivariate RR (95% CI)	
ALA						
Health Professionals Follow-up Study Leitzmann, 2004§[57] Prostate cancer excluding stage A-1	1	NR	<0.37% of energy	1.0	1.0	Age, time period, major ancestry, family history of prostate cancer, BMI at age 21, height, type 2 diabetes, vasectomy, cigarettes in past decade, vigorous physical activity, intake of total energy, % energy from protein, % energy from monounsaturated fat, % energy from saturated fat, % energy from *trans* unsaturated fats, and intakes of calcium, supplemental vitamin E and lycopene.
	2	NR	0.37-0.43% of energy	1.08 NR	1.04 (0.89, 1.22)	
	3	NR	0.44-0.49% of energy	1.12 NR	1.05 (0.89, 1.25)	
	4	NR	0.50-0.58% of energy	1.24 NR	1.16 (0.97, 1.39)	
	5	NR	>0.58% of energy	1.11 NR	1.04 (0.85, 1.27)	
	Total 47,866			p = 0.10†	p = 0.10†	
Health Professionals Follow-up Study Leitzmann, 2004§[57] Advanced prostate cancer	1	NR	<0.37% of energy	1.0	1.0	
	2	NR	0.37-0.43% of energy	1.33 NR	1.47 (1.07, 2.01)	
	3	NR	0.44-0.49% of energy	1.41 NR	1.57 (1.12, 2.21)	
	4	NR	0.50-0.58% of energy	1.53 NR	1.77 (1.24, 2.53)	
	5	NR	>0.58% of energy	1.69 NR	1.98 (1.34, 2.93)	
	Total 47,866			p = 0.0005‡	p = 0.0005†	
Netherlands Cohort Study Schuurman, 1999[39]	1	NR	0.7 g/d	1	1	Age, family history of prostate carcinoma, socioeconomic status, total energy intake, total energy-adjusted fat intake.
	2	NR	1.1 g/d	0.80 (0.59, 1..08)	0.76 (0.55, 1.05)	
	3	NR	1.3 g/d	0.82 (0.61, 1.11)	0.82 (0.60, 1.13)	
	4	NR	1.7 g/d	0.80 (0.59, 1.08)	0.80 (0.59, 1.10)	
	5	NR	2.1 g/d	0.76 (0.56, 1.03)	0.76 (0.66, 1.04)	
	Total 58,279			p = 0.04‡	p = 0.09‡	

* NR = Not Reported; † Number of people included in analysis; ‡ = test for trend.

Table 3.19 (continued). Risk of prostate cancer for different categories of consumption of omega-3 FA, by category.*

Cohort Author, Year	Study arm (quartile, quintile or dose group)	n†	Median intake	Estimates of effect				
				Age adjusted RR (95% CI)		Multivariate RR (95% CI)		Multivariate Adjustors
EPA								
Health Professionals Follow-up Study Leitzmann, 2004[57] Prostate cancer excluding stage A-1	1	NR	<0.014% of energy	1.0		1.0		Age, time period, major ancestry, family history of prostate cancer, BMI at age 21, height, type 2 diabetes, vasectomy, cigarettes in past decade, vigorous physical activity, intake of total energy, % energy from protein, % energy from monounsaturated fat, % energy from saturated fat, % energy from *trans* unsaturated fats, and intakes of calcium, supplemental vitamin E and lycopene.
	2	NR	0.014-0.027% of energy	1.14	NR	1.09	(0.93, 1.28)	
	3	NR	0.028-0.042% of energy	1.06	NR	1.02	(0.87, 1.21)	
	4	NR	0.043-0.066% of energy	1.03	NR	0.97	(0.81, 1.15)	
	5	NR	>0.066% of energy	0.92	NR	0.87	(0.72, 1.06)	
	Total 47,866			p = 0.04†			p = 0.03†	
Health Professionals Follow-up Study Leitzmann, 2004[57] Advanced prostate cancer	1	NR	<0.014% of energy	1.0		1.0		
	2	NR	0.014-0.027% of energy	1.01	NR	1.05	(0.75, 1.37)	
	3	NR	0.028-0.042% of energy	1.03	NR	0.99	(0.73, 1.35)	
	4	NR	0.043-0.066% of energy	0.89	NR	0.87	(0.63, 1.21)	
	5	NR	>0.066% of energy	0.82	NR	0.82	(0.58, 1.17)	
	Total 47,866			p = 0.08†			p = 0.18†	
Netherlands Cohort Study Schuurman, 1999[39]	1	NR	0 g/d	1		1		Age, family history of prostate carcinoma, socioeconomic status, total energy intake, total energy-adjusted fat intake.
	2	NR	0.01 g/d	0.69	(0.50, 0.95)	0.66	(0.47, 0.91)	
	3	NR	0.03 g/d	0.94	(0.69, 1.28)	0.92	(0.67, 1.27)	
	4	NR	0.05 g/d	1.06	(0.79, 1.46)	1.05	(0.77, 1.44)	
	5	NR	0.10 g/d	1.01	(0.75, 1.37)	1.00	(0.73, 1.35)	
	Total 58,279			p = 0.11‡			p = 0.10‡	

* NR = Not Reported; † Number of people included in analysis; ‡ = test for trend.

Table 3.19 (continued). Risk of prostate cancer for different categories of consumption of omega-3 FA, by category.*

Cohort Author, Year	Study arm (quartile, quintile or dose group)	n†	Median intake	Estimates of effect		Multivariate Adjustors
				Age adjusted RR (95% CI)	Multivariate RR (95% CI)	
DHA						
Health Professionals Follow-up Study Leitzmann, 2004[57] Prostate cancer excluding stage A-1	1	NR	<0.032% of energy	1.0	1.0	Age, time period, major ancestry, family history of prostate cancer, BMI at age 21, height, type 2 diabetes, vasectomy, cigarettes in past decade, vigorous physical activity, intake of total energy, % energy from protein, % energy from monounsaturated fat, % energy from saturated fat, % energy from *trans* unsaturated fats, and intakes of calcium, supplemental vitamin E and lycopene.
	2	NR	0.032-0.053% of energy	1.16 NR	1.13 (0.96, 1.33)	
	3	NR	0.054-0.079% of energy	1.03 NR	0.99 (0.83, 1.17)	
	4	NR	0.080-0.122% of energy	1.03 NR	0.99 (0.83, 1.19)	
	5	NR	>0.122% of energy	1.03 NR	1.02 (0.84, 1.25)	
	Total 47,866			p = 0.63†	p = 0.77†	
Health Professionals Follow-up Study Leitzmann, 2004[57] Advanced prostate cancer	1	NR	<0.032% of energy	1.0	1.0	
	2	NR	0.032-0.053% of energy	0.84 NR	0.79 (0.58, 1.07)	
	3	NR	0.054-0.079% of energy	0.91 NR	0.84 (0.62, 1.15)	
	4	NR	0.080-0.122% of energy	0.86 NR	0.82 (0.59, 1.13)	
	5	NR	>0.122% of energy	0.73 NR	0.71 (0.49, 1.08)	
	Total 47,866			p = 0.06†	p = 0.13†	
Netherlands Cohort Study Schuurman, 1999[39]	1	NR	0.01 g/d	1	1	Age, family history of prostate carcinoma, socioeconomic status, total energy intake, total energy-adjusted fat intake.
	2	NR	0.03 g/d	0.82 (0.60, 1.13)	0.81 (0.58, 1.11)	
	3	NR	0.06 g/d	1.01 (0.74, 1.38)	1.00 (0.73, 1.38)	
	4	NR	0.09 g/d	1.07 (0.79, 1.46)	1.09 (0.80, 1.49)	
	5	NR	0.18 g/d	1.05 (0.77, 1.42)	1.03 (0.75, 1.40)	
	Total 58,279			p = 0.19‡	p = 0.19‡	

* NR = Not Reported; † Number of people included in analysis; ‡ = test for trend; § Update of data reported in Giovannucci.[29]

Table 3.20. Relationship between methodologic quality and applicability for estimates of effect of omega-3 fatty acid consumption on risk of prostate cancer.*

Cohort Author, Year	Applicability	Quality Parameters				
		Adjustment for confounders	Blinding	Valid ascertainment, cases	Valid ascertainment, exposure	Withdrawals and dropouts described
Hawaii Health Surveillance Program LeMarchand, 1994[27]	II	Yes	NR	Yes	Yes	Yes
Health Professionals Follow-up Study Augustsson, 2003[28] Giovannucci, 1993[29] Leitzmann[57]	II	Yes	Yes	Yes	Yes	Yes
Seventh-day Adventist Mills, 1989[50]	III	Yes	NR	Yes	Yes	Yes
Swedish Twin Registry Terry, 2001[53]	III	Yes	NR	Yes	Yes	Yes
Netherlands Cohort Study Schuurman, 1999[39]	II	Yes	NR	Yes	Yes	Yes

* NR = Not Reported.

Skin Cancer (Basal Cell Carcinoma)

Overall effect. We identified one study[31] that evaluated the effect of omega-3 FA on the incidence of skin cancer. This study assessed incidence of basal cell carcinoma relative to omega-3 FA consumption. Relative to subjects in the lowest quartile of omega-3 fat consumption, subjects in the highest quartile of consumption had a small but statistically significant increase in the risk of basal cell carcinoma (RR 1.13, 95% CI 1.01, 1.27) (Table 3.21).

Sub-populations. The study cohort comprises men enrolled in the Health Professionals Follow-up Study. Analyses of the relationship between omega-3 FA and basal cell carcinoma risk for subpopulations were not reported.

Covariates. The effects of covariates on risk associated with omega-3 FA was not reported.

Effects of dose, source, and exposure duration.

Dose: This study assessed the risk of developing basal cell carcinoma given different levels of omega-3 fat consumption and found increased risk with increased dose (p for trend = 0.008).

Source: Consumption of omega-3 fat from all food sources was assessed.

Exposure duration: This study assessed dietary intake at four time points but did not report the effect of the duration of exposure to omega-3 FA and basal cell carcinoma.

Sustainment of effect. Sustainment of effect was not assessed.

Quality and applicability. See Table 3.22.

Table 3.21. Risk of skin (BCC) cancer for different categories of consumption of omega-3 FA, by category.*

Cohort Author, Year	Study arm (quartile, quintile or dose group)	n†	Median intake	Estimates of effect				
				Age adjusted RR (95% CI)		Multivariate RR (95% CI)		Multivariate Adjustors
Omega-3								
Health Professionals Follow-up Study VanDam, 2000[31]	1	NR	0.07 g/d	1		1		Age, 2-year follow-up period, major ancestry, energy intake, BMI, hair color, frequency of routine physical examinations, cigarette smoking, mean annual solar radiation in region of residence, fat.
	2	NR	0.15 g/d	0.98	NR	0.97	(0.86, 1.09)	
	3	NR	0.24 g/d	1.07	NR	1.04	(0.93, 1.17)	
	4	NR	0.34 g/d	1.07	NR	1.05	(0.93, 1.18)	
	5	NR	0.58 g/d	1.14	NR	1.13	(1.01, 1.27)	
	Total 43,217			p = 0.003‡			p = 0.008‡	

* NR = Not Reported; † Number of people included in analysis; ‡ = test for trend.

Table 3.22. Relationship between methodologic quality and applicability for estimates of effect of omega-3 fatty acid consumption on risk of skin (BCC) cancer.

Cohort Author, Year	Applicability	Quality Parameters				
		Adjustment for confounders	Blinding	Valid ascertainment, cases	Valid ascertainment, exposure	Withdrawals and dropouts described
Health Professionals Follow-up Study VanDam, 2000[31]	**II**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**

Stomach Cancer

Overall effect. We identified one study[26] that evaluated the effect of omega-3 FA on the incidence of stomach cancer. This study assessed incidence relative to fish consumption and found no association with the incidence of stomach cancer (Table 3.23).

Sub-populations. This study performed stratified analyses for men and women and found no association between fish consumption and stomach cancer risk for either group.

Covariates. The effects of covariates on risk associated with omega-3 FA were not reported.

Effects of dose, source, and exposure duration.

Dose: This study assessed the risk of developing stomach cancer, given different levels of fish consumption, and found no dose response.

Source: No association between consumption and stomach cancer incidence was found for fresh fish, processed fish, or cuttle fish.

Exposure duration: This study assessed dietary intake at baseline only.

Sustainment of effect. Sustainment of effect was not assessed.

Quality and applicability. See Table 3.24.

Table 3.23. Risk of stomach cancer for different categories of consumption of omega-3 FA, by category.*

Cohort Author, Year	Study arm (quartile, quintile or dose group)	n†	Median intake	Estimates of effect			Multivariate Adjustors
				Age adjusted RR (95% CI)	Multivariate RR (95% CI)		
Fish							
Ngoan, 2002[26] Stomach cancer *including* first 3 years follow-up Fukuoka Prefecture Cohort, Japan	1	NR	Low	NR	1		Age, sex, smoking, processed meat, liver, cooking or salad oil, suimono and pickled food.
	2	NR	Medium	NR	1.1	(0.5, 2.3)	
	3	NR	High	NR	1.0	(0.4, 2.2)	
	Total 13,000					p = 0.05‡	
Ngoan, 2002[26] Stomach cancer *excluding* first 3 years follow-up Fukuoka Prefecture Cohort, Japan	1	NR	Low	NR	1		
	2	NR	Medium	NR	0.9	(0.4, 2.2)	
	3	NR	High	NR	0.9	(0.3, 2.1)	
	Total 13,000					p = 0.05‡	

* NR = Not Reported; † Number of people included in analysis; ‡ = test for trend.

Table 3.24. Relationship between methodologic quality and applicability for estimates of effect of omega-3 fatty acid consumption on risk of stomach cancer.*

Cohort Author, Year	Applicability	Quality Parameters				
		Adjustment for confounders	Blinding	Valid ascertainment, cases	Valid ascertainment, exposure	Withdrawals and dropouts described
Fukuoka Prefecture Cohort, Japan Ngoan, 2002[26]	**II**	**Yes**	**NR**	**NR**	**Yes**	**NR**

* NR = Not Reported.

Modification of Effects of Omega-3 Fatty Acids on Tumor Incidence

None of the studies identified assessed antioxidants, the immune system, or genes for omega-3 transportation as modifiers of the effects of omega-3 FA.

Effects on Clinical Outcomes After Cancer Treatment

In reviewing the literature for this section of the report, we identified some studies for which comparisons across study arms could be used to assess the effect of omega-3 FA *alone* and others for which the effect of omega-3 FA *in combination with arginine and RNA* were assessed. In the following subsections, we describe the pooled effects of omega-3 FA alone, the pooled effect of omega-3 FA in combination with arginine and RNA, and the effect of pooling all of the studies.

Cancer Surgery: Post-operative Complications

Overall effect. The effect of omega-3 FA on post-operative complications (any outcome specifically described as a "post-operative complication") was described in fourteen studies; three for omega-3 FA alone[61-63] and 11 for omega-3 FA in combination with arginine and RNA.[64-74] Each of these studies assessed the effect of supplementation with omega-3 FA on post-operative complications in patients who underwent surgery for the resection of an upper gastrointestinal tract malignancy. The pooled random effects estimate of the risk of post-operative complications for omega-3 FA relative to placebo was 1.19 (95% CI: 0.66-2.13) (Table 3.25). The pooled random effects estimate of the risk of post-operative complications for omega-3 FA in combination with arginine and RNA relative to placebo was 0.51 (95% CI: 0.40-0.64) (Table 3.26). Pooling the studies that assessed the effect of omega-3 alone with the studies that assessed the effect of omega-3 in combination with arginine and RNA, the random effects estimate was 0.57 (95% CI: 0.46-0.71) (Figure 3.13).

Sub-populations. The effects of omega-3 FA on subpopulations were not assessed in these studies.

Covariates. The effects of covariates were not assessed.

Effects of dose, source, and exposure duration. Different doses of omega-3 FA were not compared in the studies. In all cases, the source of omega-3 FA was an enteral supplement and the duration of therapy was under two weeks.

Sustainment of Effect. The studies assessed the effect of omega-3 FA from five to ten days after therapy. Sustainment of effect was not assessed.

Quality and applicability. Among studies that entered the meta-analysis, none had both an applicability rating of I (representative of general adult population with cancer), and a summary

quality score of A (Jadad score = 5 with concealment of allocation) (Table 3.27). All of the studies had an applicability rating of II because the study samples consisted of a specific subgroup of cancer patients, i.e., patients with gastrointestinal cancer. Nearly half of the studies were of poor methodologic quality, with summary quality scores of C (Jadad score <=2, concealment of allocation not performed or reported) (Table 3.27).

Table 3.25. Relative risk of postoperative complications after cancer surgery for subjects treated with omega-3 FA compared to placebo.

	Intervention		Control		
Trial	**Source**	**n**	**Source**	**n**	**Relative Risk (95% CI)**
Kenler, 1996[61]	Fish oil, Soybean oil, Canola oil	17	Soybean oil, Osmolite	18	0.91 (0.38, 2.16)
McCarter, 1998[62]	Standard + Arginine + Omega-3	13	Standard + Arginine	14	1.35 (0.46, 3.95)
Swails, 1997[63]	Fish oil, Canola oil, Soybean oil	8	Corn oil, Soybean oil	10	1.67 (0.52, 5.39)
Pooled Random Effects Estimate*					1.19 (0.66, 2.13)

*Chi-squared test of heterogeneity p-value = 0.69.

Table 3.26. Relative risk of postoperative complications after cancer surgery for subjects treated with omega-3 FA in combination with arginine and RNA compared to placebo.

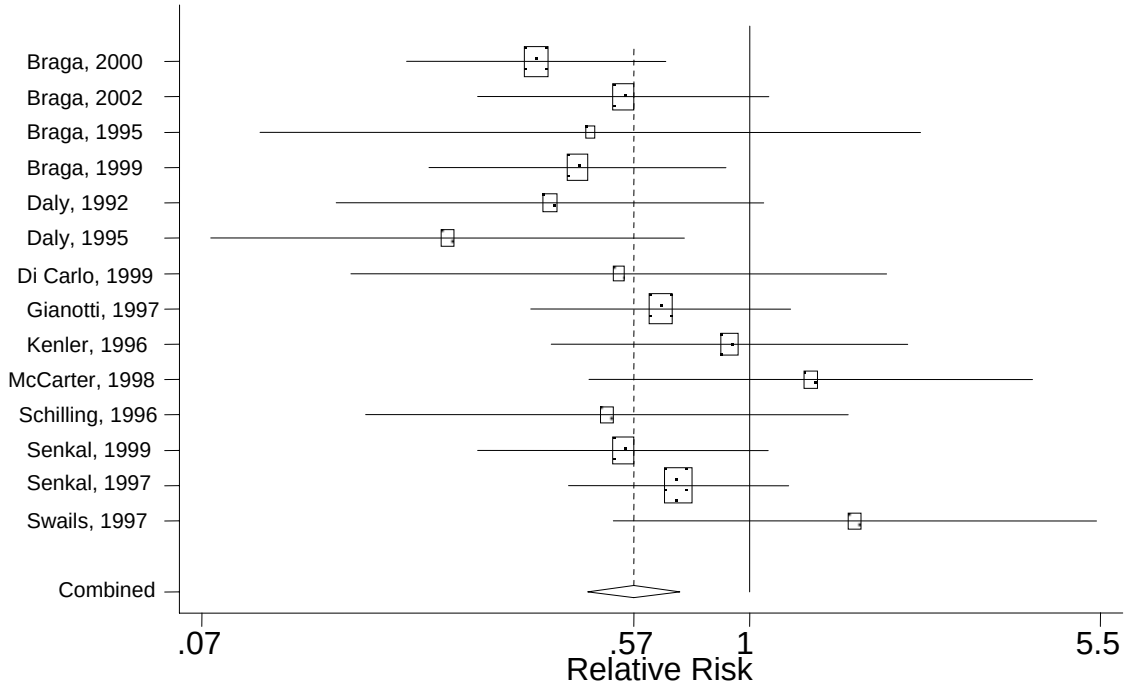
	Intervention		Control		
Trial	**Source**	**n**	**Source**	**n**	**Relative Risk (95% CI)**
Braga, 2002[64]	Omega-3, arginine, RNA	100	Standard hospital diet or isoenergetic control diet	100	0.35 (0.19, 0.67)
Braga, 2002[65]	Omega-3, arginine, RNA	50	Standard enteral diet	100	0.54 (0.27, 1.10)
Braga, 1995[66]	Omega-3, arginine, RNA	26	Standard enteral diet	24	0.46 (0.09, 2.30)
Braga, 1999[67]	Omega-3, arginine, RNA	85	Isoenergetic control diet	86	0.43 (0.21, 0.89)
Daly, 1992[68]	Omega-3, arginine, RNA	36	Standard enteral diet	41	0.38 (0.13, 1.07)
Daly, 1995[69]	Omega-3, arginine, RNA	30	Standard enteral diet	30	0.23 (0.07, 0.73)
Di Carlo, 1999[70]	Omega-3, arginine, RNA	33	Standard enteral diet	35	0.53 (0.14, 1.95)
Gianotti, 1997[71]	Omega-3, arginine, RNA	87	Standard enteral diet	87	0.65 (0.35, 1.22)
Schilling, 1996[72]	Omega-3, arginine, RNA	14	Standard enteral diet	14	0.50 (0.15, 1.61)
Senkal, 1999[73]	Omega-3, arginine, RNA	78	Standard enteral diet	76	0.54 (0.27, 1.10)
Senkal, 1997[74]	Omega-3, arginine, RNA	77	Standard enteral diet	77	0.71 (0.41, 1.21)
Pooled Random Effects Estimate*					0.51 (0.40, 0.64)

*Chi-squared test of heterogeneity p = 0.84.

Table 3.27. Relationship between methodologic quality and applicability for estimates of effect of omega-3 fatty acid consumption on post-operative complications among people with cancer.

Methodological Quality				
Applicability		A	B	C
	I			
	II		Daly, 1992[68] Daly, 1995[69] Braga, 2002[64] Braga, 2002[65] Braga, 1999[67] McCarter, 1998[62] Senkal, 1999[73] Senkal, 1997[74]	Kenler, 1996[61] Braga, 1995[66] Gianotti, 1997[71] Di Carlo, 1999[70] Schilling, 1996[72] Swails, 1997[63]
	III			

Figure 3.13. Relative risk of post-operative complications associated with omega-3 fatty acid supplementation (omega-3 alone or omega-3 in combination with arginine and RNA) among subjects who underwent resection of malignant tumor.*



* Chi-squared test of heterogeneity p-value = 0.42.

Cancer Surgery: Length of Stay

Overall Effect. The effect of omega-3 FA on length of stay was described in thirteen studies; three for omega-3 alone[61, 62, 75] and ten for omega-3 in combination with arginine and RNA.[64-66, 68-74] Each of these studies assessed the effect of supplementation with omega-3 FA on length of stay in the hospital after surgery for the resection of an upper gastrointestinal tract malignancy. The pooled random effects estimate of the mean difference between omega-3 FA and placebo for length of hospital stay is 1.09 days (95% CI: -3.63, 5.81) (Table 3.28) The pooled random effects estimate of the mean difference between omega-3 FA in combination with arginine and RNA and placebo for length of hospital stay is –3.33 days (95% CI: -4.29, -2.38) (Table 3.29). Pooling the studies that assessed the effect of omega-3 FA alone with the studies that assessed the effect of omega-3 FA in combination with arginine and RNA, the random effects estimate was –3.17 days (95% CI: -4.11, -2.26) (Figure 3.14).

Sub-populations. The effects of omega-3 FA on subpopulations were not assessed in these studies.

Covariates. The effects of covariates were not assessed.

Effects of dose, source, and exposure duration. Different doses of omega-3 FA were not compared in the studies. In all cases, the source of omega-3 fatty acid was an enteral supplement and the duration of therapy was under two weeks.

Sustainment of effect. The studies assessed the effect of omega-3 FA from seven to ten days after therapy. Sustainment of effect was not assessed.

Quality and applicability. Among studies that entered the meta-analysis, none had both an applicability rating of I (representative of general adult population with cancer), and a summary quality score of A (Jadad score = 5 with concealment of allocation) (Table 3.30). All of the studies had an applicability rating of II because the study samples consisted of a specific subgroup of cancer patients, i.e., patients with gastrointestinal cancer. One study was of the highest methodologic quality, with a Jadad score of 5 and reporting of concealment of allocation. Nearly half of the studies were of poor methodologic quality, with summary quality scores of C (Jadad score <=2, concealment of allocation not performed or reported) (Table 3.30).

Table 3.28. Mean difference of length of stay for subjects treated with omega-3 FA compared to placebo.

	Intervention		Control		Length of stay in days
Trial	**Source**	**n**	**Source**	**n**	**Mean difference (95% CI)**
Heller, 2004[75]	TPN with omega-3	24	TPN	20	0.3 (-25.2, 25.8)
Kenler, 1996[61]	Fish oil, Soybean oil, Canola oil	17	Soybean oil, Osmolite	18	0.7 (-5.1, 6.5)
McCarter, 1998[62]	Standard + Arginine + Omega-3	13	Standard + Arginine	14	2.0 (-6.5, 10.5)
Pooled Random Effects Estimate*					1 (-3.6, 5.8)

*Chi-squared test of heterogeneity p-value = 0.97.

Table 3.29. Mean difference of length of stay for subjects treated with omega-3 FA in combination with arginine and RNA compared to placebo.

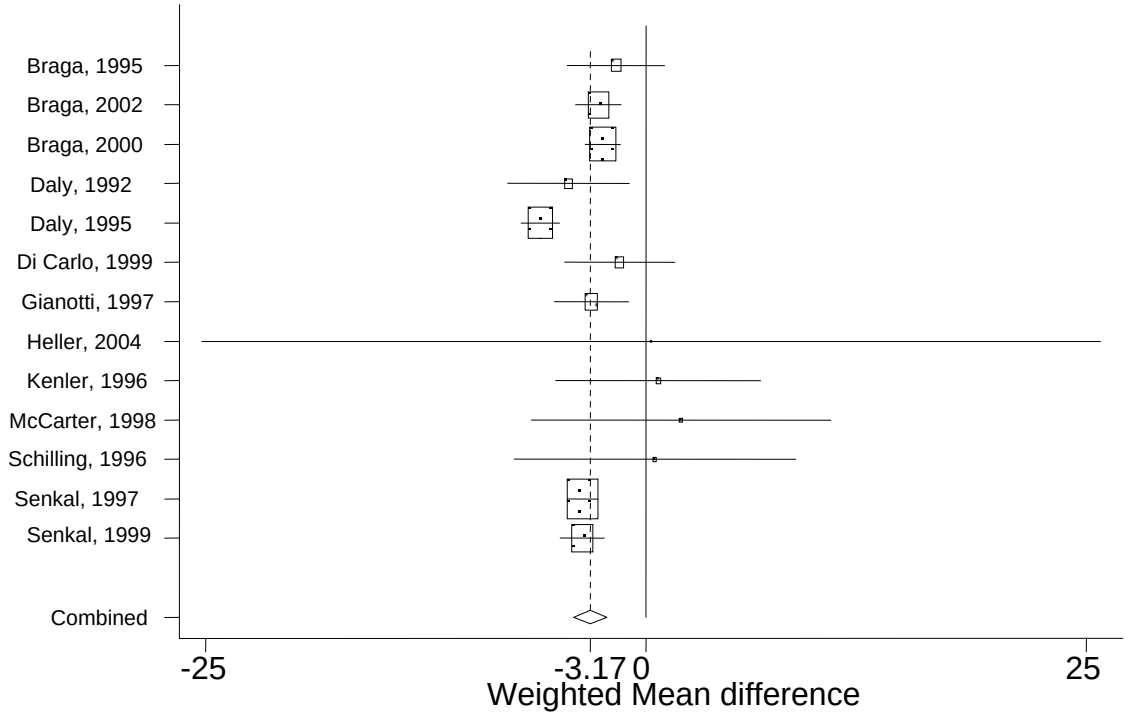
	Intervention		Control		Length of stay in days
Trial	**Source**	**n**	**Source**	**n**	**Mean difference (95% CI)**
Braga, 1995[66]	Omega-3, arginine, RNA	100	Standard hospital diet or isoenergetic control diet	100	-1.70 (-4.47, 1.07)
Braga, 2002[64]	Omega-3, arginine, RNA	50	Standard enteral diet	100	-2.45 (-3.46, -1.44)
Braga, 2002[65]	Omega-3, arginine, RNA	26	Standard enteral diet	24	-2.70 (-3.99, -1.41)
Daly, 1995[69]	Omega-3, arginine, RNA	36	Standard enteral diet	41	-6.00 (-7.09, -4.91)
Daly, 1992[68]	Omega-3, arginine, RNA	30	Standard enteral diet	30	-4.40 (-7.85, -0.95)
Di Carlo, 1999[70]	Omega-3, arginine, RNA	33	Standard enteral diet	35	-1.50 (-4.62, 1.62)
Gianotti, 1997[71]	Omega-3, arginine, RNA	87	Standard enteral diet	87	-3.10 (-5.21, -0.99)
Schilling, 1996[72]	Omega-3, arginine, RNA	14	Standard enteral diet	14	0.50 (-7.50, 8.50)
Senkal, 1999[73]	Omega-3, arginine, RNA	78	Standard enteral diet	76	-3.60 (-4.85, -2.35)
Senkal, 1997[74]	Omega-3, arginine, RNA	77	Standard enteral diet	77	-3.60 (-4.46, -2.74)
Pooled Random Effects Estimate*					-3.33 (-4.29, -2.38)

* Chi-squared test of heterogeneity p-value = 0.001.

Table 3.30. Relationship between methodologic quality and applicability for estimates of effect of omega-3 fatty acid consumption on length of stay among people with cancer.

		Methodological Quality		
		A	B	C
Applicability	I		Heller, 2004[75]	
	II		Daly, 1992[68] Daly, 1995[69] Braga, 2002[64] Braga, 2002[65] McCarter, 1998[62] Senkal, 1999[73] Senkal, 1997[74]	Kenler, 1996[61] Braga, 1995[66] Gianotti, 1997[71] Di Carlo, 1999[70] Schilling, 1996[72]
	III			

Figure 3.14. Mean difference in hospital length of stay after malignant tumor resection surgery for subjects treated with omega-3 fatty acid supplementation (omega-3 alone or omega-3 in combination with arginine and RNA) compared to subjects not treated with supplementation.*



* Chi-squared test of heterogeneity p-value = 0.001.

Cancer Surgery: Mortality

Overall effect. The effect of omega-3 FA on mortality was described in ten studies; four for omega-3 FA alone[61-63, 76] and six for omega-3 in combination with arginine and RNA.[64, 65, 68, 70, 71, 74] Each of these studies assessed the effect of supplementation with omega-3 FA on mortality after surgery for the resection of an upper gastrointestinal tract malignancy. The pooled random effects estimate for the risk of death for subjects treated with omega-3 FA relative to placebo is 1.42 (95% CI: 0.63, 3.38) (Table 3.31). The pooled random effects estimate for the risk of death for subjects treated with omega-3 FA in combination with arginine and RNA relative to placebo is 1.01 (95% CI: 0.31, 3.35) (Table 3.32). Combining all studies, the pooled random effects estimate for the risk of death is 1.25 (95% CI: 0.64, 2.48; chi-squared test of heterogeneity p = 0.43). The follow-up period ranged from seven days to eight weeks.

Sub-populations. Analyses of the effects of omega-3 FA on subpopulations were not assessed in these studies.

Covariates. The effects of covariates were not assessed in any of the studies.

Effects of dose, source, and exposure duration. Different doses of omega-3 FA were not compared in the studies. In all cases, the source of omega-3 fatty acid was an enteral supplement and the duration of therapy was under two weeks.

Sustainment of effect. The studies assessed the effect of omega-3 FA from seven days to eight weeks after therapy. Sustainment of effect was not assessed.

Quality and applicability. Among studies that entered the meta-analysis, none had both an applicability rating of I (representative of general adult population with cancer), and a summary quality score of A (Jadad score = 5 with concealment of allocation) (Table 3.33). All of the studies had an applicability rating of II because the study samples consisted of a specific subgroup of cancer patients, i.e., patients with gastrointestinal cancer. One study was of the highest methodologic quality, with a Jadad score of 5 and reporting of concealment of allocation. Nearly half of the studies were of poor methodologic quality, with summary quality scores of C (Jadad score <=2, concealment of allocation not performed or reported) (Table 3.33).

Table 3.31. Odds ratio of mortality for subjects treated with omega-3 FA compared to placebo.

	Intervention		Control		Deaths		
Trial	**Source**	**n**	**Source**	**n**	**Intervention**	**Control**	**Odds Ratio (95% CI)**
Fearon, 2003[76]	N3 FA	95	Isoenergetic control diet	105	16	11	-
Kenler, 1996[61]	Fish oil, Soybean oil, Canola oil	17	Soybean oil, Osmolite	18	0	1	-
McCarter, 1998[62]	Enteral standard diet, Arginine, Omega-3	13	Enteral standard diet, Arginine	14	0	1	-
Swails, 1997[63]	Fish oil, Canola oil, Soybean oil	8	Corn oil, Soybean oil	10	0	0	-
Pooled Random Effects Estimate*							1.67 (0.71, 4.04)

*Chi-squared test of heterogeneity p = 0.17.

Table 3.32. Odds ratio of mortality for subjects treated with omega-3 FA in combination with arginine and RNA compared to placebo.

	Intervention		Control		Deaths		
Trial	**Source**	**n**	**Source**	**n**	**Intervention**	**Control**	**Odds Ratio (95% CI)**
Braga, 2002[64]	N3 FA, Arginine	100	Standard hospital diet, Isoenergetic control diet	100	1	1	-
Braga, 2002[65]	Enteral standard diet, N3 FA	100	Enteral standard diet	50	1	2	-
Daly, 1992[68]	EPA + DHA	36	Enteral standard diet	41	1	0	-
Di Carlo, 1999[70]	N3 FA, Arginine	33	Standard enteral formula	35	1	0	-
Gianotti, 1997[71]	N3 FA, Arginine	87	Enteral standard diet	87	1	2	-
Senkal, 1997[74]	N3 FA, Arginine, Omega6 FA	77	Isoenergetic control diet, Omega6 FA	77	3	2	-
Pooled Random Effects Estimate*							1.01 (0.31,3.35)

*Chi-squared test of heterogeneity p = 0.54.

Table 3.33. Relationship between methodologic quality and applicability for estimates of effect of omega-3 fatty acid consumption on mortality among people with cancer.

		Methodological Quality		
		A	B	C
Applicability	I			
	II	Fearon, 2003[76]	Daly, 1992[68] Braga, 2002[64] Braga, 2002[65] McCarter, 1998[62] Senkal, 1997[74]	Kenler, 1996[61] Gianotti, 1997[71] Di Carlo, 1999[70] Swails, 1997[63]
	III			

Cancer Surgery: Nutrition

Overall effect. The effect of omega-3 FA on nutrition was described in 11 studies; two for omega-3 alone[61, 63] and nine for omega-3 in combination with arginine and RNA.[66-72, 77, 78] In each of these studies, subjects underwent surgery for the resection of an upper gastrointestinal tract malignancy. The nutritional parameters assessed included caloric intake, nitrogen intake, and serum albumin, transferrin, and prealbumin. In each of the studies, subjects were randomized to either receive or not receive supplementation with omega-3 FA in the peri-operative period. Treatment duration and follow-up ranged from 7 to14 days. Values for the treatment and control groups for each of the nutritional parameters are detailed in Table 3.34. Six of the studies assessed caloric intake;[61, 63, 68-70, 72] statistically significant differences were not reported by any. Of two studies that reported nitrogen intake,[68, 69] one[68] found a significant increase among subjects who received omega-3 supplementation; the other found no significant difference between groups.[69] Among six studies that assessed albumin[66-69, 77, 78] and three that assessed transferrin levels[67-69] no significant differences between groups was found. Of six studies that assessed prealbumin,[66, 67, 69, 71, 77, 78] two found significant increases in the intervention groups.[67, 77]

Sub-populations. Analyses of the effects of omega-3 FA on subpopulations were not assessed in these studies.

Covariates. Analyses of the effects of covariates on the effect of omega-3 FA on nutritional parameters were not reported in these studies.

Effects of dose, source, and exposure duration. Different doses of omega-3 FA were not compared in the studies. In all cases, the source of omega-3 FA was an enteral supplement, and the duration of therapy was under two weeks.

Sustainment of effect. The studies assessed the effect of omega-3 FA from seven to ten days after therapy. Sustainment of effect was not assessed.

Quality and applicability. Among studies that entered the meta-analysis, none had both an applicability rating of I (representative of general adult population with cancer), and a summary quality score of A (Jadad score = 5 with concealment of allocation) (Table 3.35). All but one of the studies had an applicability rating of II because the study samples consisted of a specific subgroup of cancer patients, i.e., patients with gastrointestinal cancer. One study had an applicability rating of III, which signifies a highly selected population. None of the studies had optimal methodological quality ratings (Table 3.35).

Table 3.34. Effects of omega-3 fatty acid supplementation on nutritional parameters of subjects who underwent cancer resection therapy, by nutritional supplement*

Author, year	Intervention	Follow-up	n	Nutritional parameters				
				Mean Caloric intake, kcal/d (S.D.)	Mean Nitrogen intake, g/d (S.D.)	Mean Albumin, g/dl (S.D.)	Mean Transferrin, mg/dl (S.D.)	Mean Prealbumin, mg/dl (S.D.)
Omega-3 FA								
Kenler, 1996[61]	Soybean oil, Osmolite	7 days	18	1049.6 (78)	NR	NR	NR	NR
	Fish oil, Soybean oil, Canola Oil		17	1102.9 (78.7)	NR	NR	NR	NR
	Testing between groups			p = 0.63				
Swails, 1997[63]	Corn oil, Soybean oil	7 days	10	1047 (92)	NR	NR	NR	NR
	Fish oil, Canola oil, Soybean oil		8	1010 (100)	NR	NR	NR	NR
	Testing between groups							
Omega-3 FA in combination with arginine and RNA								
Braga, 1995[66]	Enteral standard diet	8 days	24	NR	NR	3.2 (5.6)	NR	17.3 (5.1)
	Omega-3, arginine, RNA		26	NR	NR	3.4 (5.1)	NR	20.3 (4.6)
	Difference between groups							
Braga, 1999[67]	Enteral standard diet	7 days	86	NR	NR	3.7 (3.8)	218 (52)	18 (4)
	Omega-3, arginine, RNA		85	NR	NR	3.7 (3.6)	223 (48)	23 (4)
	Difference between groups							p < 0.05
Daly, 1992[68]	Enteral standard diet	7 days	41	1285 (399)	9 (2.8)	2.0 (1.3)	152 (61)	NR
	Omega-3, arginine, RNA		36	1421 (252)	15.6 (2.8)	2.1 (1.3)	161 (73)	NR
	Testing between groups			NS	p = 0.001	NS	NS	
Daly, 1995[69]	Enteral standard diet	14 days	30	1232 (372)†	10.1 (3.1)†	3.1 (0.4)	181 (53)	17 (4)
	Omega-3, arginine, RNA		30	1067 (335)†	11.9 (4.1)†	3.1 (0.4)	190 (60)	16 (7)
	Difference between groups							

* NR = Not Reported, NS = Not Significant; † = 7 days after surgery.

Table 3.34 (continued). Effects of omega-3 fatty acid supplementation on nutritional parameters of subjects who underwent cancer resection therapy, by nutritional supplement*

Author, year	Intervention	Follow-up	n	Nutritional parameters				
				Mean Caloric intake, kcal/d (S.D.)	Mean Nitrogen intake, g/d (S.D.)	Mean Albumin, g/dl (S.D.)	Mean Transferrin, mg/dl (S.D.)	Mean Prealbumin, mg/dl (S.D.)
Di Carlo, 1999[70]	Enteral standard diet	12 days	35	1550 (350)				
	Omega-3, arginine, RNA		33	1580 (330)				
	Difference between groups			NR				
Gianotti, 1999[77]	Enteral standard diet	8 days	25			3.7 (3.9)		18 (6)
	Omega-3, arginine, RNA		25			3.7 (3.6)		26 (5)
	Difference between groups					NR		$p < 0.05$
Gianotti, 1997[71]	Enteral standard diet	8 days	87					18 (6)
	Omega-3, arginine, RNA		87					23 (5)
	Difference between groups							$p < 0.01$
Schilling, 1996[72]	Enteral standard diet	10 days	14	30.4‡				
	Omega-3, arginine, RNA		14	17.4‡				
	Difference between groups			NR				
Vignali, 1995[78]	Enteral standard diet	8 days	16			3.2 (.6)		17.3 (.5)
	Omega-3, arginine, RNA		16			3.4 (.5)		20.3 (.5)
	Difference between groups					NR		NR

* NR = Not Reported; † = 7 days after surgery; ‡ kcal/kg/day.

Table 3.35. Relationship between methodologic quality and applicability for estimates of effect of omega-3 fatty acid consumption on nutritional parameters among people with cancer.

Methodological Quality				
Applicability		A	B	C
	I			
	II		Daly, 1992[68] Daly, 1995[69] Gianotti, 1999[77] Schilling, 1996[72]	Kenler, 1996[61] Braga, 1995[66] Gianotti, 1997[71] Di Carlo, 1999[70] Swails, 1997[63] Braga, 1999[67]
	III			Vignali, 1995[78]

Cancer Surgery: Weight

Overall effect. We identified three[75, 76, 79] randomized controlled trials that evaluated the effect of omega-3 FA on weight among patients undergoing surgery for the treatment of cancer (Table 3.36). Subjects receiving omega-3 supplementation had less weight loss over eight weeks in one study,[76] less weight loss during the hospital stay[75, 79] in another study, and more weight loss over 14 days in the third study.[79] However, differences between the groups were not significant in any of the studies.

Sub-populations. Analyses of the effects of omega-3 FA on subpopulations were not assessed in these studies.

Covariates. Analyses of the effects of covariates on the effect of omega-3 FA on nutritional parameters were not reported in these studies.

Effects of dose, source, and exposure duration. Different doses of omega-3 FA were not compared in the studies. In all cases, the source of omega-3 fatty acid was an enteral supplement, and the duration of therapy was under two weeks.

Sustainment of effect. The studies assessed the effect of omega-3 FA from seven to a mean of 19 days after therapy. Sustainment of effect was not assessed.

Quality and applicability. Among studies that entered the meta-analysis, none had an applicability rating of I (representative of general adult population with cancer); all of the studies had an applicability rating of II because the study samples consisted of a specific subgroup of cancer patients, i.e., patients with gastrointestinal cancer (Table 3.37). Two of the studies had optimal methodological quality ratings and a summary quality score of A (Jadad score = 5 with concealment of allocation); one had a poor quality rating (Table 3.37).

Table 3.36. Effect of omega-3 fatty acid supplementation on weight loss after cancer surgery.

Author, year	Intervention	Follow-up	n	Mean Weight loss
Fearon, 2003[76]	Isoenergetic control diet	8 weeks	105	0.37 kg/month
	N3 FA		95	0.25 kg/month
Heller, 2004[75]	TPN without omega-3 FA	5 days	20	1.1 kg
	TPN with omega-3 FA		24	0.0 kg
Preshaw, 1979[79]	IV fluids, Amino acids	14 days	23	2.5 kg
	IV fluids, Soybean oil, Amino acids		24	3.9 kg

Table 3.37. Relationship between methodologic quality and applicability for estimates of effect of omega-3 fatty acid consumption on weight loss among people with cancer.

		Methodological Quality		
		A	B	C
Applicability	I	Heller, 2004[75]		
	II	Fearon, 2003[76]		Preshaw, 1979[79]
	III			

Cancer Chemotherapy

No studies were identified that assessed the effects of omega-3 FA on clinical outcomes after chemotherapy for cancer.

Cancer Radiation Therapy

No studies were identified that assessed the effects of omega-3 FA on clinical outcomes after radiation therapy for cancer.

Modification of Effects of Omega-3 FA on Tumor Treatment

None of the studies identified assessed antioxidants or the immune system as modifiers of the effects of omega-3 FA.

Tumor Behavior: Effects of n-3 Fatty Acids on Tumor Growth, Apoptosis, and Cell Differentiation in Animal and Cell Culture Models

The effects of omega-3 FA (n-3s) have been examined on four types of tumors in animal models: mammary (breast) tumors, colon tumors, prostate tumors, and pancreatic tumors (no review articles were found on cell culture models). Of these four types, meta-analysis has been performed only on findings regarding the growth and development of mammary tumors, and systematic analysis has been performed only on findings regarding the growth and development of colon and prostate tumors.

No meta-analyses or systematic reviews were identified that addressed the issues of differentiation or apoptosis.

The conclusions regarding growth and development will be summarized for each type of tumor, followed by the conclusions regarding differentiation and apoptosis.

Growth

Mammary tumor growth. A meta-analysis of the literature on dietary FA and mammary tumor development in rats and mice found that omega-3 FA substituted isocalorically for a non-fat nutrient in the diet were associated with a small, nonsignificant decrease in the incidence of mammary tumors induced by a variety of agents[80] (Table C.3.1, Appendix C). No studies were included on the transplantation of tumor cells into healthy animals. No conclusions could be

drawn about other aspects of tumor growth such as time to onset, tumor size, or number of tumors.

Nine nonsystematic reviews assessed studies of the influence of omega-3 FAs on mammary tumor development (Table C.3.2, Appendix C). These studies used two types of models: 1) rodents that received a carcinogen to induce a cancerous tumor agent were fed diets containing defined levels of omega-3 FAs (the model described for the meta-analysis); 2) cultured tumor cells were injected or transplanted into one of a number of strains of immune-challenged mice that were fed diets containing defined levels of omega-3 FAs. Sources of omega-3 FAs included fish oil (no further definition), menhaden oil (also a type of fish oil), perilla oil (a plant source of omega-3 FAs containing only ALA), purified DHA, purified EPA, and purified ALA. None of these reviews provided quantitative data. Reviews of studies adhering to the first model generally showed that diets in which the primary source of fat was enriched in omega-3 FAs decreased the incidence and burden of chemically induced mammary tumors in rodents compared with diets in which the source of fat was corn oil, safflower oil, or some other source enriched with omega-6 FA. No negative findings were reported. Reviews of studies adhering to the second model found that the growth rates of transplanted tumors were lower in animals maintained on omega-3 FAs.

Prostate tumor growth. Few animal models of prostate cancer exist. One systematic review of four studies found that fish oils containing high levels of EPA and DHA generally suppress prostate tumor growth in vivo and in vitro;[81] however, one of the studies found that EPA was inhibitory only at high concentrations. Thus, the authors concluded that fish oil might not decrease the risk for prostate cancer. Further, nothing is known about the possible mechanism(s) by which omega-3 FAs might alter prostate tumor development.

A nonsystematic review of two studies of the effects of omega-3 FAs (in the form of fish oil) on prostate tumor growth in nude mice found that omega-3 FAs might suppress tumor growth but only when the initial number of implanted cells was low.[82]

Colon tumor growth. Three systematic reviews were identified that reported on the effects of omega-3 FAs on colon tumor growth and development. A 1991 review considered the effects of dietary omega-3 FAs on the incidence and number of carcinogen-induced colon tumors in two strains of rats (Sprague-Dawley [S-D] and Fischer 344).[83] Among the criteria for study inclusion were the use of isocaloric diets (i.e., omega-3 FAs were substituted isocalorically for another source of fat to rule out the effect of increased dietary fat or calories) and the use of standard feeding methods (to exclude the use of gavage to introduce the fats, which would bypass normal digestion and possibly absorption mechanisms). Fourteen studies were identified that met the inclusion criteria. The majority of studies demonstrated an effect of omega-3 FAs on reducing the incidence and number of colon tumors in both strains of rats. By comparison, omega-6 FA appeared to promote tumors, but only in Fischer rats. The method used to calculate the fat content of each of the diets may not have been entirely valid, in part because many of the studies omitted information required to calculate the true dietary fat intake.

A 2002 review also assessed the effect of omega-3 FAs (among a wide variety of agents) on carcinogen-induced colon tumors in Sprague-Dawley, Fischer, and Wistar rats.[84] The review considered studies that used any of three sources of omega-3 FAs: perilla oil (alone and in combination with beta-carotene), purified DHA, and fish oil (which contains DHA and EPA). Two outcomes were examined: induction of aberrant crypt foci (ACF) (an intermediate outcome) and tumor incidence. Perilla oil (12 percent by weight) in combination with beta-carotene was one of the most potent inhibitors of ACF induction (91 percent inhibition in Fischer rats), presumably because of the ability of beta-carotene, an antioxidant, to prevent peroxidative

damage to the omega-3 FA. Perilla oil alone (12 percent by weight) and DHA (0.5 and 0.7 ml/day) also inhibited formation of ACF in Fischer rats. A diet of eight percent fish oil resulted in only a 50 percent inhibition of ACF in Wistar rats. Tumor incidence was reduced as much as 64 percent by fish oil and 52 percent by perilla oil in Fischer rats, and one study reported a reduction in tumor incidence in fish oil-fed S-D rats, but the actual incidences were not reported in the latter study. The effects of omega-3 FAs on tumor incidence were weak compared with those of many of the other agents tested, such as the COX-2 inhibitor, celecoxib; the NSAID, piroxicam; and polyethylene glycol (a detergent). What's more, the review excluded studies with only negative results.

A 2003 systematic review examined the effects of a number of putative cancer preventive agents, including omega-3 FAs, on tumor growth in the colon and small intestine in the min (multiple intestinal neoplasia) mouse model, a mutant that spontaneously develops multiple intestinal neoplasias secondary to a mutation in the Apc gene, similar to humans with familial adenomatous polyposis. Findings on the effects of omega-3 FAs were obtained from two studies. The results of one study showed that DHA reduced the incidence of small intestinal tumors in female mice but actually appeared to increase the incidence in male mice. The results of the other study showed that fish oil decreased tumor yield in the small intestine by 26 to 67 percent; however, no significant effect was observed on colon tumors.

Studies of the effects of omega-3 FAs on colon cancer were also reviewed in three non-systematic reviews. A 1991 review reported that omega-3 FAs (in the form of menhaden oil or EPA) suppressed tumor number or lowered the incidence of carcinogen-induced tumors in three strains of rats - Fischer, Sprague-Dawley (S-D), and Donryu - and in Balb/c (immune-compromised) mice injected with colon carcinoma cells.[82] A 1992 review described an additional study that used a crossover design to assess the timeframe of the inhibitory effect of fish oil on colon tumor development in rats (see *Timing*).[85]

Pancreatic tumor growth. No systematic reviews assessed the results of studies on omega-3 FAs and pancreatic tumors. One nonsystematic review reported the results of a crossover study that compared the effects of isocaloric menhaden Oil and corn oil (CO) diets and examined the effects of varying ratios of omega-3 FAs and omega-6 FA on *pre*neoplastic atypical acinar cell nodules, and assessed the timeframe of the effects on adenocarcinoma development in carcinogen-treated Wistar rats.[82] A menhaden oil diet reduced the number and size of preneoplastic lesions relative to corn oil. The effect of varying ratios is reported in the *Intake* section. The crossover findings are reported in *Timing.*

Differentiation

The process of cellular differentiation can be defined as the acquisition of traits or functions that are distinct from those of the original cells, a process that is usually associated with the cessation or slowing of cell division (as in terminal differentiation). Thus anything that stimulates or hastens differentiation would likely inhibit tumorigenesis.

One nonsystematic review considered the evidence that particular lipids might influence cellular differentiation by modifying the plasma membrane composition, in the context of a discussion of the potential role of lipids in cancer therapy.[86] HL 60 and L1210 leukemia cells as well as a line of colon cancer cells showed increased rates of chemically mediated differentiation and decreased rates of growth when incubated in the presence of DHA (compared with oleic acid). Another nonsystematic review reported that EPA and DHA increased numbers of differentiating cells in a colon tumor model.[87] Finally, omega-3 FAs were found to increase

expression of peroxisome proliferator-activated receptor (PPAR)-γ expression in nuclei of many cell types.[88] PPAR α, a member of the same family, was the first transcription factor found to be regulated by FA. Activation of PPAR-γ has been shown to increase differentiation of human breast cancer cells in culture.

Apoptosis

Apoptosis is generally defined as a process of programmed cell death, in contrast to necrosis. Tumor production may be a result of the inhibition of apoptosis. Putative mechanisms for the promotion of tumor survival and growth by prostaglandins include the inhibition of apoptosis.

Three nonsystematic reviews considered the effects of omega-3 FAs on apoptosis and the possible association with tumor development. A review of the role of nutrition in apoptosis briefly speculated that omega-3 FAs might serve to maintain normal apoptosis because they increase formation of free-radical scavenging enzymes .[89] The authors cited as two examples the stimulation of apoptosis by EPA in HL-60 cells, a line of cells cultured from a human tumor, and suppression of expression of the oncogene h-ras by fish oil in cells derived from a carcinogen-induced rat mammary tumor. The h-ras oncogene disrupts cellular processes that control apoptosis.

A second review – of the role of omega-3 FAs in autoimmunity, inflammation, carcinogenesis, and apoptosis – provided several possible models supporting the possibility that omega-3 FAs might inhibit tumorigenesis by promoting apoptosis.[87] The susceptibility of omega-3 FAs to oxidative stress (peroxidation) might be responsible for the apoptosis observed in a variety of cell culture systems. As is well known, high omega-3 FA diets increase the levels of omega-3 FAs in membrane lipids of laboratory animals as well as the requirement for antioxidants to prevent peroxidation of these lipids. This oxidative stress can induce apoptosis. Likewise, expression of the bcl-2 oncogene, an antioxidant involved in controlling apoptosis, is inhibited by omega-3 FAs in transgenic and normal mice and in vitro (HL-60 and K-562 cells), which could be the mechanism by which omega-3 FAs suppress tumor growth (via promoting apoptosis). Another gene product that regulates apoptosis, in lymphocytes, is Fas/Apo-1, a receptor that is a member of the Tumor Necrosis Factor family. Fas-L, a ligand, mediates apoptosis by cross-linking the Fas receptor. Fas-L gene expression is increased by omega-3 FAs in splenocytes, and increasing evidence suggests that tumor progression can be controlled by altering cancer cell sensitivity to Fas-mediated apoptosis in this way.

A third review assessed the evidence that diet-mediated apoptosis protects the intestinal epithelium from carcinogenic stimuli.[90] The surface of the intestinal mucosa is characterized by rapidly proliferating cells organized into structures called crypts. The proliferating cells undergo an organized process of differentiation, migration, senescence, and exfoliation. Such rapid proliferation (as well as constant exposure to food borne toxins) increases susceptibility to neoplastic mutation, yet the small intestine is among the tissue least likely to be transformed. This observation has generated considerable interest in identifying the mechanisms responsible for inhibiting such mutations. The review cites evidence from an in vitro model – a human colorectal carcinoma cell line – showing that EPA leads to cellular detachment, which in turn results in apoptosis. Evidence is also presented from an in vivo model: rats fed corn oil prior to exposure to a chemical carcinogen and then immediately switched to fish oil showed an enhancement of apoptosis and a significant decrease in the frequency of abnormal crypt foci. In both models, the effects were enhanced by glutathione depletion and inhibited by antioxidants, suggesting a role for membrane lipid peroxidation in the regulation of apoptosis.

Intake

An assessment of the relationship between n-3 intake and suppression of tumor production requires that multiple groups of subjects be fed diets with varying amounts of omega-3 FAs. Dietary n-3 intake can be manipulated in several ways: 1) maintaining the caloric and fat content of the diet by substituting omega-3 FAs for another source of fat; 2) maintaining the caloric content but not the fat content of the diet by substituting omega-3 FAs for some other nutrient(s); 3) simply supplementing the regular diet with varying amounts of a source of omega-3 FAs.

Mammary Tumors. Neither the systematic nor the nonsystematic reviews of the findings on omega-3 FAs and mammary tumor growth explicitly assessed the effects of increasing n-3 intake. However, two reviews by Cave each cited a study showing an increase in mammary tumor latency (onset) and a decrease in burden and incidence with increasing dietary n-3 content (fish oil and menhaden oil) in both carcinogen-challenged rats and mice transplanted with tumor cells.[82, 91]

Prostate Tumors. The systematic review of the findings on dietary fats and prostate cancer reported the findings of a 1996 study that showed that EPA inhibited tumor growth only at high doses and that at low doses, it promoted tumor growth; however, too few details were included in the review to ascertain whether low-dose EPA diets were in fact high-dose omega-6 diets, which would account for the tumor promoting effect. None of the nonsystematic reviews provided sufficient information to determine whether dose-response was assessed in any of the studies, although one review reported that in a study of Balb/c nude mice that received transplanted prostate tumor cells in one of two doses, fish oil retarded tumor progression only in the mice that received the lower dose of cells, which may suggest a dose effect.[82]

Colon Tumors. The systematic review of findings on omega-3 FAs and colon cancer in the min mouse model found no dose-response effect for omega-3 FAs.[92] The data reported in the systematic review of findings on numerous agents by the same group precluded determination of the existence of a dose-response effect on tumor reduction in rats, because only the largest reported effect was included for each study.[84]

The 1991 nonsystematic review by Cave included several studies that assessed dose effects on tumor incidence and number in carcinogen-challenged Fischer rats and tumor size in Balb/c mice injected with colon carcinoma cells.[82] This review presented findings suggestive of a possible dose effect for omega-3 FAs, but the data were insufficient to distinguish a dose-response effect from a threshold effect for high doses. A 1996 nonsystematic review reported that an omega-3 to omega-6 ratio of one prevented tumor proliferation and decreased incidence in carcinogen-challenged mice, a finding that argues for a more complex relationship between dietary omega-3 content and tumor growth.[93] However, descriptions of study details were incomplete.

Pancreatic Tumors. A nonsystematic review of dietary fats and pancreatic cancer identified a study that found that increasing the ratio of omega-3 FAs to omega-6 FAs resulted in a decrease in development of preneoplastic atypical acinar cell nodules.[82] These findings further support the idea that it is the relative intake of omega-3 FAs that is important, rather than the absolute dietary levels.

Timing. The real question regarding a temporal relationship is whether diet exerts modulating effects during initiation or promotion of tumor development. None of the systematic reviews addressed the issue of whether the timing of dietary n-3 enrichment affected outcomes. Although the review of the effects of multiple agents on colon cancer reported the timing of diet relative to induction, no one study appeared to compare the effects of administering the agents prior to, during, and post induction. Thus, the findings that address the question of a temporal relationship are drawn from nonsystematic reviews.

Mammary Tumors. Studies that attempted to assess the timing of omega-3 FA enrichment were usually carried out with a crossover design. One crossover study reported in the 1991 Cave review found that in a mouse tumor transplant model, dietary enrichment with fish oil prior to transplantation was more effective than enrichment post-transplantation.[82] A study included in the 1997 Cave review that did not use a crossover design reported that menhaden oil lengthened the latency period for mammary tumor development both in carcinogen-challenged rats and transplanted mice, suggesting a possible temporal relationship.[91]

A 1995 review by Klurfeld related the findings of a study that suggested that studies might be more likely to report effects of mediators on promotion rather than on initiation because initiation is presumably a short period compared to promotion.[94] However, the findings reported in the Cave reviews suggest the effects of omega-3 FAs may preferentially be exerted during or even prior to initiation.

Prostate Tumors. No studies assessed the role of timing of omega-3 FA enrichment.

Colon Tumors. A 1992 review of studies on dietary fats and colon tumors included a crossover study in which rats were fed diets low or high in corn oil, or high in fish oil for nine weeks; during the last two weeks of the experimental diet, they received two weekly injections of a carcinogen.[85] Three days after the second injection, the rats were switched to a different diet or kept on the same diet for 42 additional weeks. The animals fed the fish oil diet during or after the induction phase showed a decrease in the incidence of colon tumors.

Studies in which the outcome is a precancerous condition or marker may also help address the possibility of a temporal relationship between n-3 dietary enrichment and effects on tumor development. A 1996 review included a study showing that rats that received supplemental DHA by intragastric gavage prior to carcinogenic challenge had a smaller number of and reduced development of aberrant crypt foci.[93]

Pancreatic Tumors. A study included in the 1991 review by Cave[82] compared the effects of menhaden oil- and corn oil-enriched diets initiated after carcinogenic challenge of Wistar rats on the incidence of pancreatic tumors and preneoplastic atypical acinar cell nodules. Rats that consumed high-corn oil diets for 4 months had the highest number of tumors and preneoplastic lesions, followed by those who consumed high-menhaden oil diets for two months and were then switched to high-corn oil diets. Rats that were *switched to* high-menhaden oil diets after two months and those that consumed high-menhaden oil diets for the full four months had the lowest number of tumors and preneoplastic lesions, suggesting a possible effect of diet at the time of and immediately after challenge.

Effect Modification by Genes for Omega-3 Transport

The observed effects of omega-3 FAs on tumor incidence and growth have been attributed to their involvement in the expression of a variety of genes, including those for growth factors, nuclear receptors, and oncogenes. However the response to this question limits itself to the role of gene products involved in the transport or metabolism of the omega-3 FAs themselves.

The synthesis of eicosanoids begins with the cleavage of PUFAs from membrane phospholipids via phospholipases. The metabolic pathways by which omega-3 and omega-6 FAs are then converted to the eicosanoids are regulated by two families of fast-acting and fast-turnover enzymes: the cyclooxygenases (COX) and lipoxygenases (LO) as well as cytochrome P450 monooxygenases. COX-1 is constitutively expressed and considered to be a housekeeping gene, while COX-2 is not usually detectable in normal tissues, but is induced in processes like inflammation and carcinogenesis. COX-2 controls the rate-limiting step in the synthesis of prostaglandins and thromboxanes, whereas the LO enzymes are responsible for synthesis of the leukotrienes and other products. The omega-3 and omega-6 FAs compete for the same COX and LO enzymes. Likewise, the eicosanoids derived from omega-6 FAs compete with those derived from omega-3 FAs. Prostaglandin E_2 (PGE_2), the major COX-2 metabolite of arachidonic acid, plays an important role in controlling immune function, inhibiting T-cell function and interleukin-2 production. Putative mechanisms for observed effects of omega-3 FAs on tumorigenesis that involve the PUFA transport and metabolic enzymes are included in a number of nonsystematic reviews of animal and in vitro studies (Table C.3.5, Appendix C).

Omega-3 fatty acid transport. Three nonsystematic reviews discussed the potential roles of the phospholipases in the effects of omega-3 FAs. Two reviews of studies of the effects of omega-3 FAs on cytokine production suggested that the phospholipases play a role in determining the amounts and types of eicosanoids synthesized in rodent ex vivo models.[95, 96] Similarly, a 2000 review of studies of the role of omega-3 and omega-6 FAs in potentiating angiogenesis included mention of a putative role for phospholipases but did not present specific data.[97] Angiogenesis – neovascularization – is believed to be necessary for tumor growth. Each of these reviews cited evidence that augmenting dietary omega-3 FAs resulted in replacement of phospholipid n-6s with omega-3 FAs, increasing the amount of omega-3 FAs available for action by lipases; however, no evidence was presented that omega-3 FAs are preferential substrates for phospholipases. No other reviews or reports of original research were found that dealt with the topic of omega-3 FA transport and tumor development.

Omega-3 fatty acid metabolism. Six nonsystematic reviews identified in the original literature search considered the role of n-3 metabolic enzymes in the effects of omega-3 FAs on tumorigenesis. To augment the evidence presented in these reviews, an additional brief search was conducted in Medline for the years 1999-2004 using the terms omega* AND metabolism AND cancer or tumor* and limiting the reports to reviews. A summary of one relevant 2004 review follows that of the findings of the six reviews from the original search (and summarized in Table C.3.5, Appendix C).

All six of the nonsystematic reviews from the original search that included discussion of n-3 metabolic enzymes presented evidence that dietary enrichment with omega-3 FAs inhibits the COX-2-mediated conversion of AA to PGE_2, which might, in itself, account for the effects of omega-3 FAs on tumor growth inhibition.[87, 93, 95-98] COX-2 inhibitors, such as aspirin and NSAIDS, are well known to exert a preventive effect on tumor development.[92] Rose and Connolly[97] reviewed the evidence that COX-2 is involved in the angiogenesis of tumor growth

and that the DHA-mediated inhibition of angiogenesis observed in nude mice transplanted with breast cancer cells is similar to the inhibition observed after treatment with COX-2 inhibitors. They also reviewed a series of studies using a line of human colon carcinoma cells that over-express COX-2, resulting in the stimulation of vascular endothelial cell migration and formation of capillary-like structures in culture. A review of the role of apoptosis in omega-3-mediated inhibition of tumor growth provided evidence from a variety of in vitro and in vivo models that dietary enrichment with omega-3 FAs results in a modification of COX-2 activity and a state of oxidative stress, which stimulates apoptosis.[87]

Finally, a 2004 nonsystematic review of potential mechanisms by which dietary omega-3 FAs might prevent cancer summarized the evidence for a role in the inhibition of AA-derived eicosanoids and the specific role of COX-2.[99] Omega-3 FAs inhibit synthesis of AA metabolites at three levels. First, as discussed above, high intakes of omega-3 FAs result in their incorporation into membrane phospholipids, substituting for AA and decreasing its availability for conversion to eicosanoids. Second, omega-3 FAs compete with omega-6 FAs for desaturases and elongases and have greater affinity for those enzymes than do omega-6 FAs, resulting in lower levels of AA biosynthesis. Third, omega-3 FAs themselves suppress COX-2 synthesis in chemically induced rat mammary tumors and rodent models of colon cancer and compete with omega-6 FAs for the enzyme. In addition, omega-3 FAs are a preferential substrate for COX-2. COX-2 expression has been shown to down-regulate apoptosis, and over-expression of COX-2 has been observed in models of breast, colon, and prostate cancer. Further evidence for an involvement of COX-2 includes its ability to catalyze the conversion of procarcinogens to carcinogens as well as to liberate mutagens in the metabolism of AA in *in vitro* systems.

Quality of Literature

Review Quality. Of the 36 reviews identified, only one was a meta-analysis and four others were systematic reviews, but at least one of those four excluded reports of negative findings. What's more, only three of these five reviews limited themselves to studies on PUFAs and their role in tumor development, and the studies were quite heterogeneous. Thus, two of the reviews included only one or two reports on omega-3 FAs.

Study Quality and Heterogeneity. Overshadowing the questionable quality of the reviews themselves may be the quality and heterogeneity of the studies reviewed. In vivo carcinogen-challenge studies differed in animal species and strain, forms and amounts of supplemental omega-3 FAs, method of dietary supplementation, feeding regimens (*ad lib* vs. calorie control), method of measuring dietary intake, carcinogen used, time and duration of carcinogen exposure with respect to animal age and exposure to supplemental omega-3 FAs, and outcome measures. Additionally, publication may be a particular problem with animal studies in that some journals explicitly discourage publication of negative results.

Chapter 4. Discussion

Overview

To summarize existing data about the effects of omega-3 fatty acids on cancer incidence, cancer treatment and tumor behavior, we screened over 5,000 titles, from which we reviewed 1,270 full text articles. Among these, 79 articles met our inclusion criteria including 19 randomized controlled trials, 33 prospective cohort studies and 27 reviews. These articles underwent detailed review; our main findings are summarized below.

Main Findings

Cancer Incidence

We identified 19 different cohorts for which the association between omega-3 fatty acid consumption and the incidence of one or more types of cancer had been assessed; these data were reported in 33 different publications. Omega-3 consumption was estimated based on dietary questionnaires that were typically completed once at study entry, although a few of the cohorts updated dietary intake. Omega-3 consumption was expressed as total omega-3 fatty acids, fish/marine omega-3 fatty acids or as the specific omega-3 fatty acids ALA, EPA and/or DHA. Fish consumption, which serves as a proxy for EPA and DHA consumption, was also reported in many of the studies. Across these cohorts, cancer incidence was assessed during the 3 to 24 years after dietary information was obtained and was typically ascertained using population cancer registries.

The association between omega-3 fatty acid consumption and cancer incidence was described for the following types of cancer in one or more studies: aerodigestive, bladder, breast, colorectal, lung, lymphoma, ovarian, pancreatic, prostate, skin (basal-cell) and stomach. For most of these cancers the association between omega-3 consumption and incidence was described in one study. However, associations were described in multiple studies for the following cancers: breast (7), colorectal (6), lung (4), pancreatic (2) and prostate (7).

Across the 19 cohorts for 11 different types of cancer and using up to 5 different ways to categorize omega-3 fatty acid consumption, 43 estimates of the association between omega-3 fatty acid consumption were reported. Among these, only six were statistically significant. Significant associations between omega-3 consumption and cancer risk were reported for breast cancer in two studies; for lung cancer in two; for prostate cancer in one; and for skin cancer in one. For breast cancer, one significant estimate was for increased risk, and one was for decreased risk; five other estimates did not show a significant association. For lung cancer one of the significant associations was for increased cancer risk, the other was for decreased risk and four other estimates were not significant. Only one study assessed skin cancer risk.

Considering these data together, there is no overall trend across many different cohorts and categories of omega-3 fatty acid consumption to suggest that omega-3 fatty acids reduce overall cancer risk, i.e. omega-3 fatty acids appear not to affect a mechanism of cancer development that is common across the different types of cancers evaluated in this report. Although significant associations between omega-3 fatty acids and cancer incidence were observed for several specific types of cancer, for all but one of these types of cancers and for which there were no other studies, there were many other estimates of association that were not significant. Hence, we did not identify any specific types of cancer for which the composite evidence suggests an association between omega-3 fatty acids and cancer incidence. However, for most types of cancer, the data are not sufficient to exclude with confidence an association between omega-3 fatty acid consumption and cancer incidence.

Cancer Treatment

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 treatment. Among the identified studies, the effect of omega-3 fatty acids alone could be ascertained from six studies; the effect of omega-3 fatty acids given in combination with arginine and RNA could be ascertained from 13. Effects on post-operative complications were described in 14, on hospital length of stay in 13, on mortality in ten, on nutritional parameters in 11, and on weight in three. In pooled analyses, omega-3 fatty acids had no effect compared to placebo on post-operative complications, hospital length of stay, nutritional parameters, or mortality.

Relative to a standard enteral diet, omega-3 fatty acids in combination with arginine and RNA were associated with a reduced risk of postoperative complications (RR 0.51, 95%CI 0.40, 0.64) and reduced length of hospital stay (pooled mean difference -3.33 days, 95%CI -4.29, -2.38). Among nine studies that assessed the effect on nutritional parameters omega-3 plus arginine and RNA, prealbumin was significantly higher in the omega-3 + arginine + RNA group in three studies, but not different in three others; mean nitrogen intake was significantly higher in one study but not in another. No significant differences were found for mean caloric intake, mean albumin, or mean transferrin.

Although the combination of omega-3 fatty acids, arginine, and RNA are associated with a reduced risk of post-operative complications and reduced length of hospital stay, it is not possible to ascertain whether these effects are due to omega-3 fatty acids, arginine, RNA, or a combination of these.

Tumor Behavior

We evaluated 27 reviews of studies on animals or cell culture models that described the effects of tumor growth, differentiation or apoptosis. Although much of the evidence favored a role for n-3 dietary enrichment in the inhibition or prevention of tumor growth, at least in some animal models, the quality of the reviews is not sufficient to permit strong conclusions to be drawn.

A 1995 nonsystematic review[100] and 1997 meta-analysis[101] commented on the validity of various methods of dietary fat manipulation – isocaloric substitution of omega-3 FAs or omega-6

FAs for fat nutrients, isocaloric substitution for a combination of nutrients, simple addition to a complete diet, fat restriction, or energy restriction. Ideally, the total caloric intake and fat intake should be the same across all experimental groups. The authors concluded that some effects attributed to low-fat diets or to omega-3 FAs added to a calorie-controlled diet might in fact be the result of energy restriction; some nutrition researchers have theorized that ad lib-feeding of rodents actually produces a model of obesity rather than a model of a normal weight animal subject to some dietary manipulation. In some studies, fat and energy parity were maintained by varying the ratio of omega-3 FAs to some other fat (e.g., omega-6 FAs) , whereas omega-3 FA intake was varied in other studies by substituting it for a non-fat nutrient or simply adding it to an ad lib-fed diet, thus altering the proportion of dietary fat and other nutrients and potentially altering total caloric intake. If the ability of omega-3 FAs to exert an effect depends on their ratio to omega-6 FAs in the diet, differential effectiveness would be expected from different means of supplementation.

The 1995 review[100] also commented on the variation in times of introduction and duration of n-3 supplementation relative to age and age at exposure to carcinogen. As described above, crossover studies have been used to test hypotheses regarding the stage of tumor development at which dietary fats might exert their effects; however, conclusions derived from such studies are suspect for a number of reasons. In the laboratory situation, the time of exposure to the carcinogen is known precisely. In contrast, because the causes of most human cancers are not known, the exposure time and time to onset can never be pinpointed, although it is believed that the time of onset may be many years. Thus, any substance that served to mitigate initial exposure or the events following exposure would need to be taken as a preventive and for as long as possible. None of the reviews appeared to include studies in which n-3 supplementation was initiated early in development or even much before exposure to the carcinogen.

Finally, at least one review noted that tumors induced by different carcinogens responded differently to dietary n-3 supplementation. This finding further limits the comparability and applicability of animal studies.

Limitations

The result in this report should be interpreted in the context of its limitations. The sections on cancer incidence, cancer treatment and tumor behavior have specific limitations which we detail below. Additionally, the results we report in each of these sections could be affected by publication bias or incomplete data. With regard to publication bias, for observational studies, publication bias occurs as the result of preferential publication of studies with outcomes that achieve statistical significance, with no regard for whether such outcomes were secondary in nature. Given that the results for the observational studies included in this report were all essentially negative, publication bias does not appear to be present. For the RCTs, included in this report, we found no evidence of publication bias on funnel plot analyses.

Regarding incomplete data, it is possible that additional information that would change our conclusions is available in reports that we were unable to locate or for which we were unable to find a translator. For the section on tumor behavior we were unable to obtain 22 out of 82 articles that were of potential relevance to the report. For the sections on cancer incidence and treatment, this is unlikely that our data were incomplete given that our screening strategy was broad and

that among over 1,200 articles that were of possible relevance to the report, only 28 could not be located.

Additional limitations specific to each of the sections of this report follow.

Cancer Incidence

Interpretation of the data we report are limited by differences in the characteristics of the populations that were studied in the different cohorts and by differences in the methods used to ascertain exposure to omega-3 fatty acids and tumor incidence. With regard to differences in population characteristics, differences in measured and unmeasured characteristics across cohorts could affect the estimates of effect of omega-3 fatty acids in studies relative to one another. Of particular note is the fact that omega-3 consumption varied a great deal across study cohorts. However, given that basically no effect was found in any of the cohorts, this could be regarded as evidence that omega-3 fatty acids have no effect regardless of intake amount. With regard to differences in the methods used to ascertain omega-3 fatty acid exposure, with the exception of the Health Professionals Follow-up Study and the Nurses' Health Study, all other studies assessed omega-3 exposure at a single time point. For these studies it is not know whether omega-3 fatty acid consumption remained constant over the observation period for ascertainment of cancer incidence, which ranged from 6 to 27 years. Since for these studies it is not known whether omega-3 fatty acid consumption was constant over time, the reported estimates of effect for these studies should be interpreted with caution.

Cancer Treatment

Interpretation of the results of the RCTs that assessed the effects of omega-3 fatty acids on clinical outcomes after cancer surgery is limited by the fact that the populations enrolled in these studies were highly selected and hence the results may not be generalizable to other patient populations.

Tumor Behavior

In addition to the limitations imposed on our summary of the evidence by the quality of the reviews and the quality and heterogeneity of the original research, our summary may have been further affected by several other factors. First, a paucity of the reviews included cell and tissue culture models. Second, only the 2004 review included findings that really addressed the role of genes involved in n-3 transport and metabolism, and little evidence was presented in that review regarding transport. A review of original animal and cell/tissue culture studies for the years 1999 to 2004 might provide more complete answers to that question and point the way toward possible applications to human disease prevention and treatment.

Conclusions

In a large body of literature spanning numerous cohorts from many countries and with different demographic characteristics, the evidence does not suggest a significant association between omega-3 fatty acids and cancer incidence. In a small body of literature, there is no significant association between omega-3 fatty acids and clinical outcomes after surgery for upper GI malignancy. Although a large, but heterogeneous, body of literature suggests that omega-3 dietary enrichment may play a favorable role in the inhibition or prevention of tumor growth in some animal models, the quality of the reviews is not sufficient to permit strong conclusions to be drawn.

Future Research

We offer the following 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, for specific cancer sites for which few studies have been published, and for which animal models suggest an association between omega-3 fatty acids and cancer, systematic pooling of data across existing cohorts to might be worthwhile. Likewise, 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, 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.

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Listing of Excluded Studies: Tumor Incidence and Treatment

Rejected: Search Unsuccessful (n = 28)

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Rejected No Outcomes of Interest and/or Not Able to Compare Omega-3 Effect Across Study Arms (n = 41)

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Listing of Excluded Studies: Tumor Behavior

Rejected Not Omega-3 Fatty Acids (n = 7)

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2. Carroll KK, Khor HT. Dietary fat in relation to tumorigenesis. Prog Biochem Pharmacol 1975;10:308-53.

3. Eynard AR. Is the risk of urinary tract tumorigenesis enhanced by a marginal chronic essential fatty acid deficiency (EFAD)? Nutrition 1998; 14(2):211-6.

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7. Tang DG, La E, Kern J, Kehrer JP. Fatty acid oxidation and signaling in apoptosis. Biological Chemistry 2002; 383(3-4):425-42.

Rejected Not EFA Supplementation (n = 1)

1. Eynard AR. Does chronic essential fatty acid deficiency constitute a pro-tumorigenic condition? SO - Medical Hypotheses. 48(1). 1997. 55-62.

Rejected Other Mechanisms (n = 2)

1. Carroll KK. Biological effects of fish oils in relation to chronic diseases. Lipids 1986; 21(12):731-2.
2. Cave WTJr. Dietary n-3 (omega-3) polyunsaturated fatty acid effects on animal tumorigenesis. FASEB Journal 1991; 5(8):2160-6.

Rejected Not a Review (n = 1)

1. Colas S, Paon L, Denis F *et al*. Enhanced radiosensitivity of rat autochthonous mammary tumors by dietary docosahexaenoic acid. Int J Cancer 2004; 109(3):449-54.

Rejected Not Cancer Development (n = 1)

1. Baronzio G, Freitas I, Griffini P *et al*. Omega-3 fatty acids can improve radioresponse modifying tumor interstitial pressure, blood rheology and membrane peroxidizability. SO - Anticancer Research. 14(3A). 1994. 1145-1154.

Acronyms

AA	Arachidonic acid	n-3	Omega-3
Ab	**Antibody**	n-6	Omega-6
AHRQ	**Agency for Healthcare Research and Quality**	NA	Not applicable
AI	**Adequate intake**	NHANES III	The Third National Health and Nutrition Examination
ALA	Alpha-linolenic acid	NCI	National Cancer Institute
AMDR	Acceptable macronutrient distribution ranges	NEI	National Eye Institute
ANCOVA	Analysis of covariance	NEMC	New England Medical Center
ANOVA	Analysis of variance	NHANES	National Health and Nutrition Examination
Ca	Calcium	NHLBI	National Heart, Lung and Blood Institute
CCT	Controlled clinical trial	NIAAA	National Institute of Alcohol Abuse and Alcoholism
CI	Confidence interval	NIAID	National Institute of Allergy and Infectious Diseases
CRP	C-reactive protein	NIAMS	National Institute of Arthritis and Musculoskeletal and Skin Diseases
CSFII	Continuing Food Survey of Intakes by Individuals	NICHD	National Institute of Child Health and Human Development
d	day	NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
D6D	Delta-6 Desaturase	NIH	National Institutes of Health
DGLA	Dihomo-gamma-linolenic acid	NNH	Number needed to harm
DHA	Docosahexaenoic acid	NR	Not reported
DPA	Docosapentaenoic acid	ODS	Office of Dietary Supplements
DRI	Dietary Reference Intake	PG	Prostaglandin
Ds-DNA	**Double-stranded DNA**	PGD	Prostaglandin-D
EF	**Effect size**	PGE	Prostaglandin-E
EFA	**Essential fatty acid**	PGF	Prostaglandin-F
EPA	**Eicosapentaenoic acid**	PGL	Prostaglandin-L
EPC	Evidence-Based Practice Center	PGH	Prostaglandin-H
ESR	Erythrocyte sedimentation rate	PUFA	Polyunsaturated fatty acid
FNB	Food and Nutrition Board	QRF	Quality review form
g	grams	RCT	Randomized controlled trial
GLA	Gamma-linolenic acid	RDA	Recommended daily allowances
HDL	High density lipoprotein	RXT	Randomized crossover trial
IL-1β	Interleukin 1β	Sd	Standard deviation
IOM	Institute of Medicine	SCEPC	Southern California Evidence-Based Practice Center
LA	Linoleic acid	SLE	Systemic lupus erythematosus
LC PUFA	Long-chain polyunsaturated fatty acid	SEM	Standard errors of the means
LDL	Low density lipoprotein	TEP	Technical expert panel
MA	Metaanalysis	TNF-*a*	Tumor necrosis factor-*a*
MANOVA	Multivariate analysis of variance	TX	Treatment
MeSH Term	Medical Subject Headings Term	TXA	Thromboxane-A
mg/dl	Milligrams per deciliter	UCLA	University of California, Los Angeles
min	Minutes	VLCFA	Very long chain fatty acid
Mo	Month	VLN-3FA	Very long chain n-3 fatty acids
n	Number	wk	Week

U.S. Department of Health and Human Services
Mike O. Leavitt, *Secretary*

Office of Public Health and Science
Richard H. Carmona, M.D., M.P.H., F.A.C.S., *Surgeon General of the United States*

Agency for Healthcare Research and Quality
Carolyn M. Clancy, M.D., *Director*

Appendixes for the Effects of Omega-3 Fatty Acids on Cancer

A.1 Preliminary Research Questions

Table A.1.1. Preliminary research questions.

GENERAL QUESTIONS: Questions posed for all three participating EPCs, for years 1 and 2.
1. What is the evidence that variable clinical effects may reflect differences in: • Serving size (fish vs. dietary supplement); • Source (fish, food, plant) vs. dietary supplement (fish oil, plant oil); • Specific type(s) of omega-3 fatty acids (docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA), and alpha-linolenic acid (ALA), fish, fish oil), or the ratio of omega-6/omega-3 fatty acids used; • Manufacturer (different purity, presence of other potentially active agents)? 2. What is the evidence for adverse events, side effects, or counter-indications associated with omega-3 fatty acids (DHA, EPA, DPA, ALA, fish oil, fish)? 3. What is the evidence that omega-3 fatty acids are associated with adverse events in specific subpopulations such as diabetics? 4. What are the mean and median intakes of DHA, EPA, DPA, ALA, fish, fish oil, omega-6, omega-6/omega-3 ratio in the US population? 5. What is the evidence that omega-3 fatty acids influence overall energy balance? 6. What is the evidence that accurate interpretation of the results of clinical studies is dependent on knowing the absolute fatty acid content of the baseline data, the relative fatty acid content of the baseline diet, or the tissue ratios of fatty acids (omega-6/omega-3) during the investigative period?
DISEASE-SPECIFIC QUESTIONS: Questions posed to the SCEPC for year 2 of the project.
Cancer:
A. Tumor Incidence:
A.1 What is the evidence that omega-3 fatty acids reduce the incidence of tumors? *If omega-3 fatty acids influence the incidence tumors:* A.2 For what type of tumors? A.3 Is there an inverse relationship with intake? A.4 Is there a temporal relationship with intake?
B. Tumor Behavior:
B.1 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:* B.2 For what type of tumors? B.3 Is there an inverse relationship with intake? B.4 Is there a temporal relationship with intake?
C. Modification of Omega-3 Effects:
C.1 What is the evidence that the response to omega-3 fatty acids is dependent of the intake of antioxidants such as vitamin E or other bioactive food components? C.2 What is the evidence that the response is modified by the state of the immune system? C.3 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/behavior?
D. Omega-3 Fatty Acids as Effect Modifiers:
D.1 What is the evidence that omega-3 fatty acids alter the effects of chemotherapy on malignant tumors?
E. Other:
E.1 What is the evidence that drugs influencing the cyclooxygenase activity influence tumor incidence/behavior?

A.2 Technical Expert Panel

The members of our technical expert panels are listed in Table A.2.1. We conducted our TEP meetings via teleconference on January 8, 2004. Dr. Beth Collins-Sharp, the Task Order Officer, and Dr. Kenneth Fink, Director of the Evidence-Based Practice Center Program, represented AHRQ on these calls; Dr. Anne Thurn, Director of the Evidence-Based Review Program, represented ODS; and Dr. Catherine MacLean, the Task Order Director, Sally Morton, Co-Director of the SCEPC, and Rena Hasenfeld, the Project Manager, represented the SCEPC. The key comments and recommendations of the TEP are summarized in Table A.2.2. The TEP continued to advise the SCEPC throughout the project via mail, fax, e-mail, and phone calls.

Table A.2.1 Technical expert panel members.

Cancer		
Name	**Area of Expertise**	**Institution**
William S. Harris, PhD	Omega-3 Fatty Acids	University of Missouri-Kansas City School of Medicine
Jennifer Malin, MD	Oncology	University of California, Los Angeles
Cindy Davis, PhD	Cancer	National Cancer Institute
Ralph W. Moss, PhD	Cancer	Cancer Communications, Inc.
Walter Willett, MD, MPH, Dr PH	Omega-3 Fatty Acids	Harvard Medical School

Table A.2.2. Key TEP comments and recommendations.

Cancer
<u>Cancer Question A: Tumor Incidence</u> **A.1 What is the evidence that omega-3 fatty acids reduce the incidence of tumors?** **If omega-3 fatty acids influence the incidence tumors:** **A.2 For what type of tumors?** **A.3 Is there an inverse relationship with intake?** **A.4 Is there a temporal relationship with intake?**
• Address with large cohort studies.
• All types of cancers are of interest.
• Focus on pre-cancerous and malignant tumors.
• Examine the effects of omega-3 fatty acids on individual types of cancer in order to capture differential effects.
<u>Cancer Question B: Tumor Behavior</u> **B.1 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:** **B.2 For what type of tumors?** **B.3 Is there an inverse relationship with intake?** **B.4 Is there a temporal relationship with intake?**
• Studies in humans are very limited; most studies have been performed using animals and tissue lines.
• The focus of these questions differs substantially from the others addressed in the task order; the SCEPC and AHRQ will decide whether these questions are outside of the scope and resources of the task order..
<u>Cancer Question C: Modification of Omega-3 Effects</u> **C.1 What is the evidence that the response to omega-3 fatty acids is dependent of the intake of antioxidants such as vitamin E or other bioactive food components?** **C.2 What is the evidence that the response is modified by the state of the immune system?** **C.3 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/behavior?**
• There is no standard definition of “bioactive food components.”
• There is no standard definition of “state of the immune system.”
• These questions would be based on human evidence.
<u>Cancer Question D: Omega-3 Fatty Acids as Effect Modifiers</u> **D.1 What is the evidence that omega-3 fatty acids alter the effects of chemotherapy on malignant tumors?**
• The question should be broadened to read: What is the evidence that omega-3 fatty acids alter the effects of cancer treatment on malignant tumors and clinical outcomes after cancer treatments?

Table A.2.2 (continued). Key TEP comments and recommendations.

Cancer Question E: Other **E.1 What is the evidence that drugs influencing the cyclooxygenase activity influence tumor incidence/behavior?**
• This question seems to be off of the primary target of this task order.
• The TEP recommended adding a paragraph about the effects of cyclooxygenase inhibition on cancer to the background or introduction of the report.
1. What is the evidence that variable clinical effects may reflect differences in: – **Serving size (fish vs. dietary supplement)** – **Source (fish, food, plant) vs. dietary supplement (fish oil, plant oil)** – **Specific type of omega-3 fatty acid (DHA, EPA, DPA, ALA)** – **Ratio of omega-6/omega-3** – **Manufacturer (different purity, presence of other potentially active agents)?**
• The effects of flaxseed and flaxseed oil should be specifically assessed. Even if there are no data, this should be stated in the report.
• It is important to look at ALA and long-chain fatty acids.
• It is important to look at the relative percent of fatty acids or percent of energy.
• To assess compliance with omega-3 fatty acids, tissue levels of omega-3 fatty acids can be used: there should be a 50% or double level of fatty acids among the intervention group, although this may vary by the type of tissue and baseline diet.
• If looking at tissue samples, the effect of the intervention is dependent on the baseline level of omega-3 fatty acids. The content of omega-3 fatty acids in the diet should be assessed.

A.3 Industry Experts

Table A.3.1. Industry experts that were contacted for data about efficacy of omega-3 fatty acids.

Name	Affiliation
Ian Newton	Roche Vitamins
Herb Woolf, PhD	BASF Corporation
Annette Dickinson	Council for Responsible Nutrition

Figure A.3.1. Letter sent to industry experts.

Date

Name
Address
City, State, Zip Code

Dear XXX,

I am writing on behalf of the Evidence Based Practice Centers at RAND, New England Medical Center and the University of Ottawa. We are conducting a systematic review of the efficacy and toxicity of omega-3 fatty acids in the prevention and treatment of a number of different diseases/conditions. This review is being conducted under a contract from the Agency for Healthcare Research and Quality (AHRQ).

We are contacting you to see if there is any evidence, including unpublished evidence, that you want considered. Our focus is on clinical trials of omega-3 fatty acids in humans, so animal and chemical studies are not necessary.

The specific questions that all the EPCs will address are detailed in the attachment to this letter.

Please contact me with any information that you might have.

Best regards,

Catherine MacLean, M.D., Ph.D.
RAND
1700 Main Street, M 23-C
Santa Monica, CA 90407-2138
Voice: 310 393-0411, x6364
Fax: 310-451-6930

A.4 Search Strategies

Table A.4.1. Core search strategy.

1. exp fatty acids, omega-3/
2. fatty acids, essential/
3. Dietary Fats, Unsaturated/
4. linolenic acids/
5. exp fish oils/
6. (n 3 fatty acid$ or omega 3).tw.
7. docosahexa?noic.tw,hw,rw.
8. eicosapenta?noic.tw,hw,rw.
9. alpha linolenic.tw,hw,rw.
10. (linolenate or cervonic or timnodonic).tw,hw,rw.
11. menhaden oil$.tw,hw,rw.
12. (mediterranean adj diet$).tw.
13. ((flax or flaxseed or flax seed or linseed or rape seed or rapeseed or canola or soy or soybean or walnut or mustard seed) adj2 oil$).tw.
14. (walnut$ or butternut$ or soybean$ or pumpkin seed$).tw.
15. (fish adj2 oil$).tw.
16. (cod liver oil$ or marine oil$ or marine fat$).tw.
17. (salmon or mackerel or herring or tuna or halibut or seal or seaweed or anchov$).tw.
18. (fish consumption or fish intake or (fish adj2 diet$)).tw.
19. diet$ fatty acid$.tw.
20. or/1-19
21. dietary fats/
22. (randomized controlled trial or clinical trial or controlled clinical trial or evaluation studies or multicenter study).pt.
23. random$.tw.
24. exp clinical trials/ or evaluation studies/
25. follow-up studies/ or prospective studies/
26. or/22-25
27. 21 and 26
28. (Ropufa or MaxEPA or Omacor or Efamed or ResQ or Epagis or Almarin or Coromega).tw.
29. (omega 3 or n 3).mp.
30. (polyunsaturated fat$ or pufa or dha or epa or long chain or longchain or lc$).mp.
31. 29 and 30
32. 20 or 27 or 28 or 31

Table A.4.2. Literature searches by topic.

Tumor incidence and outcomes after cancer treatment
1. exp fatty acids, omega-3/
2. fatty acids, essential/
3. Dietary Fats, Unsaturated/
4. linolenic acids/
5. exp fish oils/
6. (n 3 fatty acid$ or omega 3).tw.
7. docosahexa?noic.tw,hw,rw.
8. eicosapenta?noic.tw,hw,rw.
10. (linolenate or cervonic or timnodonic).tw,hw,rw.
11. menhaden oil$.tw,hw,rw.
12. (mediterranean adj diet$).tw.
13. ((flax or flaxseed or flax seed or linseed or rape seed or rapeseed or canola or soy or soybean or walnut or mustard seed) adj2 oil$).tw.
14. (walnut$ or butternut$ or soybean$ or pumpkin seed$).tw.
15. (fish adj2 oil$).tw.
16. (cod liver oil$ or marine oil$ or marine fat$).tw.
17. (salmon or mackerel or herring or tuna or halibut or seal or seaweed or anchov$).tw.
18. (fish consumption or fish intake or (fish adj2 diet$)).tw.
19. diet$ fatty acid$.tw.
20. or/1-19
21. dietary fats/
22. (randomized controlled trial or clinical trial or controlled clinical trial or evaluation studies or multicenter study).pt.
23. random$.tw.
24. exp clinical trials/ or evaluation studies/
25. follow-up studies/ or prospective studies/
26. or/22-25
27. 21 and 26
28. (Ropufa or MaxEPA or Omacor or Efamed or ResQ or Epagis or Almarin or Coromega).tw.
29. (omega 3 or n 3).mp.
30. (polyunsaturated fat$ or pufa or dha or epa or long chain or longchain or lc$).mp.
31. 29 and 30
32. 20 or 27 or 28 or 31
33. exp neoplasms/
34. (neoplasm$ or cancer$ or tumour$ or tumor$ or carcinoma$ or malignanc$).tw.
35. 33 or 34
36. 32 and 35

Table A.4.2 (continued). Literature searches by topic.

Tumor Behavior
1. (EICOSAPENTAENOIC ACID or DOCOSAHEXAENOIC ACID).sh. or "Nutrition/Lipids (1972-) [13222]".cc. or "Metabolism/Lipids [13006]".cc. or "Biochemical Studies/Lipids [10066]".cc.
2. dietary fat.sh.
3. plant oils.sh.
4. exp fatty acids, omega-3/
5. fatty acids, essential/
6. Dietary Fats, Unsaturated/
7. linolenic acids/
8. exp fish oils/
9. (n 3 fatty acid$ or omega 3).tw.
10. docosahexa?noic.tw,hw,rw.
11. eicosapenta?noic.tw,hw,rw.
12. alpha linolenic.tw,hw,rw.
13. (linolenate or cervonic or timnodonic).tw,hw,rw.
14. menhaden oil$.tw,hw,rw.
15. (mediterranean adj diet$).tw.
16. ((flax or flaxseed or flax seed or linseed or rape seed or rapeseed or canola or soy or soybean or walnut or mustard seed) adj2 oil$).tw.
17. (walnut$ or butternut$ or soybean$ or pumpkin seed$).tw.
18. (fish adj2 oil$).tw.
19. (cod liver oil$ or marine oil$ or marine fat$).tw.
20. (salmon or mackerel or herring or tuna or halibut or seal or seaweed or anchov$).tw.
21. (fish consumption or fish intake or (fish adj2 diet$)).tw.
22. diet$ fatty acid$.tw.
23. dietary fats/
24. (Ropufa or MaxEPA or Omacor or Efamed or ResQ or Epagis or Almarin or Coromega).tw.
25. (omega 3 or n 3).mp.
26. Gamma-linolenic acid/
27. (n 6 fatty acid$ or omega 6).tw.
28. octadecadienoic.tw,hw,rw.
29. linoleic.tw,hw,rw.
30. linoleate.tw,hw,rw.
31. ((olive or safflower or cottonseed or sesame or sesame seed or corn or borage or primrose or black currant or vegetable) adj2 oil$).tw.
32. arachidonic.tw,hw,rw.
33. or/1-32
34. neoplasm.sh.
35. neoplastic disease.sh.
36. (neoplasm$ or cancer$ or tumour$ or tumor$ or carcinoma$ or malignanc$).tw.
37. or/34-36
38. 33 and 37
39. limit 38 to animal
40. limit 39 to review

A.5 Inclusion/Exclusion Criteria

Table A.5.1. Inclusion/Exclusion Criteria at Screening Stage for Cancer.*

Assessed the effect of omega-3 fatty acids on cancer
Presented research on human subjects; presented research on human subjects and animals for apoptosis, tumor growth, and differentiation questions only.
Reported the results of randomized or controlled clinical trials or prospective cohort studies;† reported the results of review articles and meta-analyses of animal studies and cell culture studies for apoptosis, tumor growth, and differentiation questions only.‡

* Language was not a barrier to inclusion; † We defined a randomized controlled trial (RCT) as one in which the participants were assigned to one of two (or more) study groups using a process of random allocation (e.g., random number generation, coin flips); we defined a controlled clinical trial (CCT) as one in which participants were either: (1) assigned to one of two (or more) study groups using a quasi-random allocation method (e.g., alternation, date of birth, patient identifier), or (2) possibly assigned to one of two (or more) study groups using a process of random or quasi-random allocation; ‡ We defined a review article as one that summarizes a number of different studies and may draw conclusions about a particular intervention. The methods used to identify, select and appraise the studies are not systematic or necessarily reproducible. (Any review article that is not clearly a systematic review or a meta-analysis is a "review.") The summary in a review is generally narrative; We defined a systematic review as a review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research, and to collect and analyze data from the studies that are included in the review. Statistical methods are not used to analyze and summarize the results of the included studies; We defined a meta-analysis as a systematic review that uses statistical methods to integrate the results of the individual studies. A meta-analysis contains at least one estimate formed by pooling results across individual studies, i.e., an overall odds ratio.

A.6 Evidence Grading System

Table A.6.1. Summary Score for Methodologic Quality.

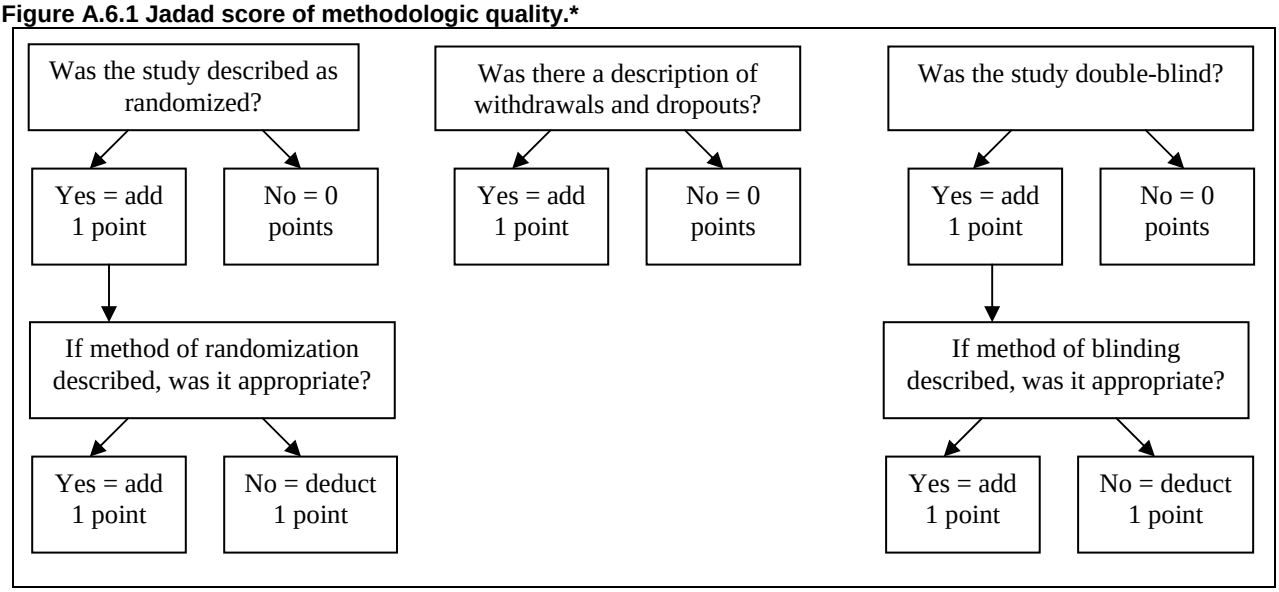
Summary Score	Jadad Score	Concealment of Allocation
A	5	Performed
B	5	Not performed, or Not reported
	3 or 4	Performed, Not performed, or Not reported
	0,1, or 2	Performed
C	0, 1, or 2	Not performed or not reported

Even though a study may focus on a specific target population, limited study size, eligibility criteria and patient recruitment process may result in a narrow population sample that is of limited applicability, even to the target population. To capture this parameter, we categorize studies into the applicability scale described in Table A.6.1.

Table A.6.2 Applicability ratings.

Applicability		**Health state**
I	Sample is representative of the U.S. population.	A General population. Typical healthy people similar to Americans without known cardiovascular diseases.
II	Sample is representative of a relevant sub-group of the target population, but not the entire population. For example, a study that is restricted to women or a fish oil study in Japan where the background diet is very different from that of the US would fall into this category.	B Diseased population. Subjects with cancer.
III	Sample is representative of a narrow subgroup of subjects only, and not well applicable to other subgroups. For example, a study of oldest old men or a study of a population on highly controlled diet.	

Figure A.6.1 Jadad score of methodologic quality.*



***** Jadad A, Moore A, Carrol D, et al. Assessing the quality of reports of randomized clinical trials: Is blinding necessary? Control Clin Trials. 1996;17:1-12.

A.7 External Peer Reviewers

Table A.7.1. Peer Reviewers.

Peer Reviewer	Area of Expertise	Affiliation
Judith Ashley, Ph.D., M.S.P.H., R.D.	Nutrition	University of Nevada, Reno
Bruce Bistrian, M.D., Ph.D.	Cancer	Harvard
Manuela Gago, M.D., Ph.D.	Cancer	University of Southern California
Heinz-Josef Lenz, M.D	Cancer	University of Southern California

Figure B.1. Literature Screener Form.

Article ID

Reviewers: Assigned on:

2. **Author:**
Title:
Cite:

3. Reviewer: _____

4. Research Topic: (**circle one**)
Omega 3 or synonymous topic 1
Unclear, no English abstract 8
(**If unclear, skip to question 10 on language**)
None of the above ..... 9 (**STOP**)

5. Condition(s)/Subject(s) studied: (**check all that apply**)
- Cancer ..... □
- Cognitive function (>=45) ..... □
- Neurological disease ..... □

None of the above ..... □ (**STOP**)

6. Study population: (**check all that apply**)
Human ..... □
Animal ..... □ (**STOP**)
Unclear ..... □ (**STOP**)
Other ..... □ (**STOP**)

7. Study design: (**circle one**)
Descriptive (historical, editorial, etc.) ..... 1 (**STOP**)
Review/meta-analysis ..... 2 (**STOP**)
Randomized clinical trial 3
Controlled clinical trial (quasi-randomization) 4
Non-randomized clinical trial 5
Cohort/Case control 6
Case series (≥ 10) 7
Case report (≥ 10) ..... 8 (**STOP**)
Other (specify: _____) ..... 9 (**STOP**)

8. Type of disease: (**check all that apply**)
CANCER:
Skin □
Oral cavity and pharynx ..... □
Colorectal ..... □
Other gastrointestinal ..... □
Lung and bronchus ..... □
Other respiratory ..... □
Bone and soft tissue ..... □
Breast ..... □
Female genital ..... □
Urinary system ..... □
Lymphoma ..... □
Leukemia ..... □
Pre-cancerous ..... □
Other cancer ..... □

NEURO: (**check all that apply**)
Amyotrophic lateral sclerosis (ALS) ..... □
Dementia: Alzheimer's Disease ..... □
Dementia: Multi-Infarct ..... □
Dementia: Vascular ..... □
Dementia: NOS ..... □
Epilepsy ..... □
Guillain-Barré Syndrome ..... □
Huntington's Disease ..... □
Multiple sclerosis ..... □
Neuromyelitis optica (Devic's syndrome) ..... □
Optic Neuritis ..... □
Parkinson's Disease ..... □
Peroxisomal Biogenesis Disorders/Leukodystrophies ..... □
(Zellweger Syndrome, Metachromatic Leukodystrophy, Alexander Disease, Infantile Refsum Disease)
Other neuro ..... □

9. Does the study describe the effects of Omega-3 FA on:
CANCER:
Cancer incidence ..... □
Tumor growth ..... □
Tumor differentiation ..... □
Apoptosis ..... □
Chemotherapy ..... □
Mortality/Survival ..... □
Other cancer outcomes ..... □
NEURO:
Incidence of neuro disease ..... □
Outcomes of neuro disease ..... □
Cognitive function ..... □
NONE OF THE ABOVE ..... □

10. Language of article: (**circle one**)
English 1
German 2
French 3
Italian 4
Danish 5
Russian 6
Spanish 7
Other (specify: _____) 8

11. Do you think this article might be a duplicate or include the same data as another study?
No 1
Yes 2
If yes, which one(s)? _____
(enter article ID, author, or 9999 for "don't know.")

12. Is there a reference that needs to be checked?
No 1
Yes 2
If yes, which one(s)? _____
(enter article ID, author, or 9999 for "don't know.")

Notes:

Article ID:_____ Reviewer:_____

First Author: _____
(Last Name Only)

Study Number: ___of____Description:_____
(Enter '1of 1' if only one) (if more than one study)

1. Design: (CIRCLE ONE)

RCT.....1
RXT 2
CCT.....3
Cohort 4
Case control (**STOP** if Cancer) 5
Case series ≥ 10 (**STOP** if Cancer) 6
Other design .....7 (STOP)

2. Is there a difference in Omega-3 content between arms:
(CIRCLE ONE)

Yes 1
Not applicable (Case control & case series) 2
No.....3 (STOP)
Unclear.....8 (STOP)

3. Is Omega-3 measured in any of the following ways?
(CIRCLE ONE)

Diet.....1
Tissue 2
Diet and Tissue 3
None of the above.....4

4. If the study reports on cognitive function, is the age of the population 45 or older?
(CIRCLE ONE)

Yes 1
Study not on cognitive function.....2
No.....3 (STOP)
Unclear.....8 (STOP)

IF THE STUDY DESIGN IS COHORT, CASE CONTROL, OR CASE SERIES PLEASE SKIP TO QUESTION 12.

5. Is the study described as randomized? (CIRCLE ONE)
   Yes 1
   No..... 2

6. If the study was randomized, was method of randomization appropriate? (CIRCLE ONE)
   Yes 1
   No..... 2
   Method not described..... 8
   Not applicable (not randomized)..... 9

7. Is the study described as: (CIRCLE ONE)
   Double blind.....1
   Single blind, patient 2
   Single blind, outcome assessment 3
   Open.....4
   Blinding not described 8
   Not applicable 9

8. If reported, was the method of double blinding appropriate? (CIRCLE ONE)
   Yes 1
   No.....2
   Double blinding method not described 8
   Not applicable 9

9. If study was randomized, did the method of randomization provide for concealment of allocation? (CIRCLE ONE)
   Yes 1
   No..... 2
   Concealment not described 8
   Not applicable (not randomized)..... 9

10. Are withdrawals (W) and dropouts (D) described? (CIRCLE ONE)

Yes, reason described for **all** W and D 1
Yes, reason described for **some** W and D..... 2
Not described 8
Not applicable 9

11. If the design is crossover, please note the duration of the following periods:

Please enter the number and code in the appropriate box.

Period	Number	Unit	Units
X-Over			1. Hour 2. Day 3. Week 4. Month 5. Year 8. ND 9. NA
Run-In			
Wash-Out			

12. Does the study population represent any of the following characteristics? (CHECK ALL THAT APPLY)

	Healthy	Diseased
Typical people	❑	❑
Atypical people (in terms of diet, SES, other factors)	❑	❑
Narrow, atypical people (including highly controlled diet)	❑	❑
Cannot categorize (incomplete data)	❑	❑

13. What was the study's funding source? (CHECK ALL THAT APPLY)

Government..... ❑
Hospital..... ❑
Industry ..... ❑
Private (non-industry) ..... ❑
Unclear ..... ❑
Not described ..... ❑

Other (code(s): _____) ..... ❑

14. What was the number of sites involved in the study?
(Enter number or 99 if not reported)

___ ___

15. In what country was the study conducted? (CHECK ALL THAT APPLY)

Australia..... ❑
Denmark..... ❑
Germany..... ❑
Italy ..... ❑
Japan ..... ❑
Netherlands ..... ❑
Russia..... ❑
UK..... ❑
US ..... ❑
Other (enter code) ..... ❑

____ ____, ____ ____, ____ ____, ____ ____

Not specified ..... ❑

16. What was the racial/ethnic population studied?
(Check all that apply)

Caucasian ..... ❑
African Ancestry ..... ❑
Hispanic ..... ❑
Asian ..... ❑
Native American ..... ❑
Eskimo/Intuit ..... ❑
Other (enter code): ..... ❑

_____ _____ , _____ _____ , _____ _____
Not described ..... ❑

17. What was the percent of male participants?
(Enter number or 999)

___ ___ ___ %

18. What was reported for the following questions regarding subjects ages? (Enter number 99 for not reported)

Mean Age..... ____ ____
Median Age..... ____ ____
Age Range..... ____ ____ to ___ ____

19. What were the study's inclusion criteria?
(Enter code or 99 if NR)

Enter code: ____ ____, ____ ____, ____ ___, ____ ____

____ ____, ____ ____, ____ ___, ____ ____

20. What were the study's exclusion criteria?
(Enter code or 99 if NR)

Enter code: ____ ____, ____ ____, ____ ___, ____ ____

____ ____, ____ ____, ____ ___, ____ ____

21. Was a validated dietary assessment method described?
(CIRCLE ONE)

Yes 1
No..... 2
Not described 8
Not applicable 9

22. Was the omega 3 fatty acid content described in the baseline diet?
(CIRCLE ONE)

Yes (please answer Q23)..... 1
No (please SKIP Q23)..... 2
Not applicable (not RCT or CCT, SKIP Q23) 9

23. If the omega 3 content was described in the baseline diet, please specify the quantification:

(Example: Fish 8 grams per week, please use codes for source and units.)

Source (code)	Number (Enter #)	Source Unit (code)	Time Unit (code)

Source Units
1. grams 6. tabs
2. oz 7. ml
3. mg 8. other
4. servings 9. ND
5. caps

Time Units
1. hour 5. year
2. day 6. ND
3. week
4. month

Interventions (for all study designs)

24. Enter sample size and intervention/exposure data for each arm beginning with placebo or control, then in order of first mention.

For observational studies answer only columns denoted with asterisks (*):

Arm/ Group	Sample size *	Components *	Total Dose	Units	Frequency	Is omega 3 quantified?	Duration of treatment *	Units *	Co-intervention(s) or Co-exposure(s)
1	P PY _____ CNTRL N ENTERING CASES _____ N COMPLETING	_____ _____ _____ _____ _____ _____	_____	_____	_____	Total O3 ..... ❑ ALA..... ❑ DHA ..... ❑ EPA ..... ❑ DPA..... ❑ Not Reported . ❑ Not Applicable ❑	_____	_____	_____ _____ _____ _____ _____ _____
2	P PY _____ CNTRL N ENTERING CASES _____ N COMPLETING	_____ _____ _____ _____ _____ _____	_____	_____	_____	Total O3 ..... ❑ ALA..... ❑ DHA ..... ❑ EPA ..... ❑ DPA..... ❑ Not Reported . ❑ Not Applicable ❑	_____	_____	_____ _____ _____ _____ _____ _____
3	P PY _____ CNTRL N ENTERING CASES _____ N COMPLETING	_____ _____ _____ _____ _____ _____	_____	_____	_____	Total O3 ..... ❑ ALA..... ❑ DHA ..... ❑ EPA ..... ❑ DPA..... ❑ Not Reported . ❑ Not Applicable ❑	_____	_____	_____ _____ _____ _____ _____ _____
4	P PY _____ CNTRL N ENTERING CASES _____ N COMPLETING	_____ _____ _____ _____ _____ _____	_____	_____	_____	Total O3 ..... ❑ ALA..... ❑ DHA ..... ❑ EPA ..... ❑ DPA..... ❑ Not Reported . ❑ Not Applicable ❑	_____	_____	_____ _____ _____ _____ _____ _____

Appendix B. Coding/Data Abstraction Forms (continued)

Arm/ Group	Sample size *	Components *	Total Dose	Units	Frequency	Is omega 3 quantified?	Duration of treatment *	Units *	Co-intervention(s) or Co-exposure(s)
	Enter a number for N entering and N completing or enter 9999 if not reported. If observational study, circle appropriate unit of measurement: P Persons PY People years CNTRL Control CASES Cases	Enter code(s)	Enter # or 997. Variable 999. Not reported	Enter a number 1. g 2. mg 3. oz 4. kcal	Enter a number 1.Hour 2.Day 3.Week 4.Month 5.Year 8.ND 9. NA	Enter a number 1.Yes 2.No 8.ND 9.NA	Enter a number 997. Variable 998. ND 999. NA	Enter a number 1.Hour 2.Day 3.Week 4.Month 5.Year 8.ND 9. NA	Enter code(s) Bioactive markers begin at code 100.
5	P PY _____ CNTRL N ENTERING CASES _____ N COMPLETING	_____ _____ _____ _____ _____ _____	_____	_____	_____	Total O3 ..... ❑ ALA..... ❑ DHA ..... ❑ EPA ..... ❑ DPA..... ❑ Not Reported . ❑ Not Applicable ❑	_____	_____	_____ _____ _____ _____ _____ _____
6	P PY _____ CNTRL N ENTERING CASES _____ N COMPLETING	_____ _____ _____ _____ _____ _____	_____	_____	_____	Total O3 ..... ❑ ALA..... ❑ DHA ..... ❑ EPA ..... ❑ DPA..... ❑ Not Reported . ❑ Not Applicable ❑	_____	_____	_____ _____ _____ _____ _____ _____
7	P PY _____ CNTRL N ENTERING CASES _____ N COMPLETING	_____ _____ _____ _____ _____ _____	_____	_____	_____	Total O3 ..... ❑ ALA..... ❑ DHA ..... ❑ EPA ..... ❑ DPA..... ❑ Not Reported . ❑ Not Applicable ❑	_____	_____	_____ _____ _____ _____ _____ _____
8	P PY _____ CNTRL N ENTERING CASES _____ N COMPLETING	_____ _____ _____ _____ _____ _____	_____	_____	_____	Total O3 ..... ❑ ALA..... ❑ DHA ..... ❑ EPA ..... ❑ DPA..... ❑ Not Reported . ❑ Not Applicable ❑	_____	_____	_____ _____ _____ _____ _____ _____

Appendix B. Coding/Data Abstraction Forms (continued)

Arm/ Group	Sample size *	Components *	Total Dose	Units	Frequency	Is omega 3 quantified?	Duration of treatment *	Units *	Co-intervention(s) or Co-exposure(s)
	Enter a number for N entering and N completing or enter 9999 if not reported. If observational study, circle appropriate unit of measurement: P Persons PY People years CNTRL Control CASES Cases	Enter code(s)	Enter # or 997. Variable 999. Not reported	Enter a number 1. g 2. mg 3. oz 4. kcal	Enter a number 1.Hour 2.Day 3.Week 4.Month 5.Year 8.ND 9. NA	Enter a number 1.Yes 2.No 8.ND 9.NA	Enter a number 997. Variable 998. ND 999. NA	Enter a number 1.Hour 2.Day 3.Week 4.Month 5.Year 8.ND 9. NA	Enter code(s) Bioactive markers begin at code 100.
9	P PY CNTRL _____ N ENTERING CASES _____ N COMPLETING	_____ _____ _____ _____ _____ _____	_____	_____	_____	Total O3 ..... ❑ ALA..... ❑ DHA ..... ❑ EPA ..... ❑ DPA..... ❑ Not Reported . ❑ Not Applicable ❑	_____	_____	_____ _____ _____ _____ _____ _____
10	P PY CNTRL _____ N ENTERING CASES _____ N COMPLETING	_____ _____ _____ _____ _____ _____	_____	_____	_____	Total O3 ..... ❑ ALA..... ❑ DHA ..... ❑ EPA ..... ❑ DPA..... ❑ Not Reported . ❑ Not Applicable ❑	_____	_____	_____ _____ _____ _____ _____ _____
11	P PY CNTRL _____ N ENTERING CASES _____ N COMPLETING	_____ _____ _____ _____ _____ _____	_____	_____	_____	Total O3 ..... ❑ ALA..... ❑ DHA ..... ❑ EPA ..... ❑ DPA..... ❑ Not Reported . ❑ Not Applicable ❑	_____	_____	_____ _____ _____ _____ _____ _____
12	P PY CNTRL _____ N ENTERING CASES _____ N COMPLETING	_____ _____ _____ _____ _____ _____	_____	_____	_____	Total O3 ..... ❑ ALA..... ❑ DHA ..... ❑ EPA ..... ❑ DPA..... ❑ Not Reported . ❑ Not Applicable ❑	_____	_____	_____ _____ _____ _____ _____ _____

Arm/ Group	Sample size *	Components *	Total Dose	Units	Frequency	Is omega 3 quantified?	Duration of treatment *	Units *	Co-intervention(s) or Co-exposure(s)
	Enter a number for N entering and N completing or enter 9999 if not reported. If observational study, circle appropriate unit of measurement: P Persons PY People years CNTRL Control CASES Cases	Enter code(s)	Enter # or 997. Variable 999. Not reported	Enter a number 1. g 2. mg 3. oz 4. kcal	Enter a number 1.Hour 2.Day 3.Week 4.Month 5.Year 8.ND 9. NA	Enter a number 1.Yes 2.No 8.ND 9.NA	Enter a number 997. Variable 998. ND 999. NA	Enter a number 1.Hour 2.Day 3.Week 4.Month 5.Year 8.ND 9. NA	Enter code(s) Bioactive markers begin at code 100.

Case report /Case series/Cohort specific questions

Instructions: For case report, case series, and cohort studies ONLY, please fill out this page (Q25-Q29), otherwise SKIP to Q30.

25. Were case controls identified from any of the following locations:

(CHECK ALL THAT APPLY)

Community ..... ☐
Hospital ..... ☐
Health care system (non-hospital) ..... ☐
Nursing home ..... ☐
Not described ..... ☐
Not Applicable (cohort studies) ..... ☐

26. Was there blinded assessment of the following:

(CIRCLE ONE FOR EACH ROW)

	YES	NO	N/A
Eligibility of cases and controls/ Or exposed vs. unexposed	1	2	3
Assessment of outcome	1	2	3
Assessment of exposure	1	2	3

27. In the analysis, was any attempt made to adjust for known confounders, not included in matching?

(CIRCLE ONE)

Yes 1
No 2

28. Were cases and controls matched by any of the following characteristics?

(CHECK ALL THAT APPLY)

Age ..... ☐
Sex ..... ☐
Underlying neurological disease ..... ☐
Cognitive function ..... ☐

Educational level.....□
Other characteristics.....□

Not matched.....□
Not applicable.....□

29. Was ascertainment of cases valid? **(CIRCLE ONE)**

Yes 1
No..... 2

Outcomes

30. Please enter the type of outcomes measured. For case series, case report, or cohort enter the outcome that defines the study:

Enter code for each outcome measured:	Enter code(s) for each set of adjustments made for each outcome measured.: (Please separate with commas)		

31. Overall, was a validated method used for ascertainment of clinical outcomes?

(CIRCLE ONE)

Yes.....1
No.....2
Not applicable.....9

Evaluation

32. When, relative to the start of the intervention or exposure, were outcomes reported?

(Enter the number/code in the appropriate box)

	Number	Unit
1st follow-up		
2nd follow-up		
3rd follow-up		
4th follow-up		
5th follow-up		
6th follow-up		
Additional follow-ups		

Units

1. Hour	5. Year
2. Day	8. ND
3. Week	9. NA
4. Month	997. Variable

33. What was the total duration of the study?

_____ (Number) _____ (Units: use codes from above)

Adverse Events

34. Were any of the following adverse events mentioned?

(Check all that apply)

Clinical bleeding..... ❑
Dermatological..... ❑
Diarrhea..... ❑

GI complaint or nausea..... ❑
Headaches..... ❑
Withdrawal due to adverse event..... ❑

Other adverse events..... ❑
No Adverse events..... ❑

Not described..... ❑
Not applicable..... ❑

For CANCER studies only, answer Q35-37.
If not a cancer study then SKIP.

35. Is the state of the immune system described?

(CIRCLE ONE)

Yes.....1
No.....2

36. Are the effects of omega 3 fatty acids on the outcomes of any of the following reported?

(Check all that apply)

Cancer surgery..... ❑
Chemotherapy..... ❑
Radiation..... ❑
None of the above..... ❑

37. Does the study describe genes involved in omega 3 fatty acid transport or metabolism?

(CIRCLE ONE)

Yes.....1
No.....2

Appendix B. Coding/Data Abstraction Forms (continued)

Appendix C. Evidence Tables

Table C.1.1. Evidence table of the effects of omega-3 fatty acids on the risk of developing cancer in cohort studies, by cancer type.*

Cohort First Author, Year	Study Characteristics	Duration:	Eligibility criteria	Type of cancer: Ascertainment:	Applicability Funding source Quality
Aerodigestive Cancer					
Honolulu Heart Program Chyou, 1995[32]	Sample size† (people/person-years): 8,002/NR py Age (mean/range): NR/45-68 Race: Asian % male: 100 # sites: 1 Location: Hawaii	Duration: 24 years	Inclusion: Institutionalized American men of Japanese ancestry residing on Oahu. Exclusion: Prevalent aerodigestive cancer at enrollment.	Type: oral cavity and pharynx, other gastrointestinal Ascertainment: Oahu hospitalizations for cancer and Hawaii Tumor Registry (part of NCI SEER Program)	Applicability: III Funding source: Government Quality: Adjustment for confounders: Y Blinded to exposure/outcome: NR Valid ascertainment of outcome: Y Valid ascertainment of exposure: Y Description of withdrawals and dropouts: Y
Bladder Cancer					
Honolulu Heart Program Chyou, 1993[33]	Sample size† people/person-years): 7,995/NR Age (mean/range): NR/45-68 Race: Asian % male: 100 # sites: 1 Location: Hawaii	Duration: 22 years	Inclusion: Institutionalized American men of Japanese ancestry residing on Oahu. Exclusion: Prevalent bladder cancer at enrollment.	Type: Bladder Ascertainment: Oahu hospitalizations for cancer and Hawaii Tumor Registry (part of NCI SEER Program)	Applicability: III Funding source: Government Quality: Adjustment for confounders: Y Blinded to exposure/outcome: NR Valid ascertainment of outcome: Y Valid ascertainment of exposure: Y Description of withdrawals and dropouts: Y

*NR = not reported; Y = yes; N = no; py = person years; † Number of people in cohort who met inclusion criteria for analysis of specified type of cancer.

Appendix C. Evidence Tables (continued)

Table C.1.1. Evidence table of the effects of omega-3 fatty acids on the risk of developing cancer in cohort studies, by cancer type.*

	Study Characteristics	Duration:	Eligibility criteria	Type of cancer: Ascertainment:	Applicability Funding source Quality
Breast Cancer					
Diet, Cancer and Health Study Stripp, 2003[55]	Sample size: 23, 693 people Age (mean/range): NR/50-65 Race: NR % male: 0 # sites: 1 Location: Denmark	Duration: 5 years	Inclusion: Age 50-60/Born in Denmark Exclusion: Cancer diagnosis as per Danish Cancer Registry	Type: Breast Ascertainment: Danish Cancer Registry; Danish Breast Cancer Co-operative Group	Applicability: II Funding source: Private Non-Industry Quality: Adjustment for confounders: Y Blinded to exposure/outcome: NR Valid ascertainment of outcome: Y Valid ascertainment of exposure: Y Description of withdrawals and dropouts: Y
Life Span Study Key, 1999[52]	Sample size† people/person-years): 34,759/488,989 py Age (mean/range): NR/NR Race: NR % male: NR # sites: 1 Location: Japan	Duration: 12 years	Inclusion: Survivors of atomic bomb in Hiroshima or Nagasaki, Japan that were alive on September 1, 1969. Exclusion: Prevalent breast cancer at baseline.	Type: breast Ascertainment: Hiroshima and Nagasaki cancer Registries	Applicability: III Funding source: Government Quality: Adjustment for confounders: Y Blinded to exposure/outcome: NR Valid ascertainment of outcome: Y Valid ascertainment of exposure: Y Description of withdrawals and dropouts: Y
Netherlands Cohort Study Voorrips, 2002[37]	Sample size† people/person-years): 1,598/NR Age (mean/range): NR/55-69	Duration: 6 years	Inclusion: Population born between 1917 and 1931.	Type: breast Ascertainment: Regional cancer	Applicability: II Funding source: Government Quality: Adjustment for confounders: Y

Appendix C. Evidence Tables (continued)

Table C.1.1. Evidence table of the effects of omega-3 fatty acids on the risk of developing cancer in cohort studies, by cancer type.*

	Race: NR % male: NR # sites: 1 Location: Netherlands		Exclusion: Prevalent cancer at baseline, incomplete dietary data.	registries	Blinded to exposure/outcome: Y Valid ascertainment of outcome: Y Valid ascertainment of exposure: Y Description of withdrawals and dropouts: Y
Norwegian National Health Screening Service Cohort Vatten, 1990[41]	Sample size† people/person-years): 14,500/161,013 py Age (mean/range): NR/35-51 Race: NR % male: NR # sites: 1 Location: Norway	Duration: 14 years	Inclusion: Population of Norway born between 1925 and 1942. Exclusion: Prevalent cancer, including breast cancer, at baseline, incomplete questionnaires.	Type: breast Ascertainment: National Cancer Registry	Applicability: II Funding source: NR Quality: Adjustment for confounders: Y Blinded to exposure/outcome: NR Valid ascertainment of outcome: Y Valid ascertainment of exposure: Y Description of withdrawals and dropouts: Y
Nurses' Health Study Holmes, 2003[43] Holmes, 1999[44]	Sample size† people/person-years): 88,795/1,172,028 py (1980-1994) 88,647/NR py (1980-1998) Age (mean/range): 47/30-55 Race: NR % male: NR # sites: 1 Location: US	Duration: 18 years	Inclusion: US female nurses born between 1921 and 1946. Exclusion: Prevalent breast cancer at baseline.	Type: breast Ascertainment: self-report or vital records confirmed by medical records review	Applicability: II Funding source: Government Quality: Adjustment for confounders: Y Blinded to exposure/outcome: Y Valid ascertainment of outcome: Y Valid ascertainment of exposure: Y Description of withdrawals and dropouts: Y

*NR = not reported; Y = yes; N = no; py = person years; † Number of people in cohort who met inclusion criteria for analysis of specified type of cancer.

Appendix C. Evidence Tables (continued)

Table C.1.1. Evidence table of the effects of omega-3 fatty acids on the risk of developing cancer in cohort studies, by cancer type.*

Cohort First Author, Year	Study Characteristics	Duration:	Eligibility criteria	Type of cancer: Ascertainment:	Applicability Funding source Quality
Singapore Chinese Health Study Gago-Dominguez, 2003[51]	Sample size† people/person-years): 34,734/NR py Age (mean/range): NR/45-74 Race: NR % male: NR # sites: 1 Location: Singapore	Duration: 7 years	Inclusion: Permanent residents or citizens of Singapore living in government housing estates‡ speaking Hokkien or Cantonese born between 1919 and 1953. Exclusion: Previous cancer history.	Type: breast Ascertainment: Singapore Cancer registry	Applicability: II Funding source: NR Quality: Adjustment for confounders: Y Blinded to exposure/outcome: NR Valid ascertainment of outcome: Y Valid ascertainment of exposure: Y Description of withdrawals and dropouts: N

*NR = not reported; Y = yes; N = no; py = person years; † Number of people in cohort who met inclusion criteria for analysis of specified type of cancer; ‡ 86% of population lived in this type of housing at the time the cohort was formed.

Appendix C. Evidence Tables (continued)

Table C.1.1. Evidence table of the effects of omega-3 fatty acids on the risk of developing cancer in cohort studies, by cancer type.*

Cohort First Author, Year	Study Characteristics	Duration:	Eligibility criteria	Type of cancer: Ascertainment:	Applicability Funding source Quality
Colorectal Cancer					
HealthProfessionals Follow-up Study Giovannucci, 1994[30]	Sample size† people/person-years): 47,949/264,680 py Age (mean/range): NR/40-75 Race: Caucasian, Black, Asian % male: 100 # sites: 1 Location: US	Duration: 6 years	Inclusion: Male dentists, optometrists, osteopaths, podiatrists, pharmacists, and veterinarians born between 1911 and 1946 that responded to a postal questionnaire. Exclusion: Cancer (other than non-melanoma skin cancer)/Incomplete food frequency questionnaire.	Type: colorectal Ascertainment: self-report or vital records confirmed by medical records review	Applicability: II Funding source: Government and private (non-industry) Quality: Adjustment for confounders: Y Blinded to exposure/outcome: Y Valid ascertainment of outcome: Y Valid ascertainment of exposure: Y Description of withdrawals and dropouts: Y
Iowa Women's Health Study Bostick, 1994[34]	Sample size† people/person-years): 35,215/167,447 py Age (mean/range): 62/55-69 Race: Caucasian % male: NR # sites: 1 Location: US	Duration: 5 years	Inclusion: Women with valid Iowa driver's license born between 1917 and 1931. Exclusion: Cancer (other than non-melanoma skin cancer)/Incomplete food frequency questionnaire/Dietary questionnaire with implausible total energy intake.	Type: colorectal Ascertainment: State Health Registry of Iowa	Applicability: II Funding source: Government Quality: Adjustment for confounders: Y Blinded to exposure/outcome: NR Valid ascertainment of outcome: Y Valid ascertainment of exposure: Y Description of withdrawals and dropouts: Y

*NR = not reported; Y = yes; N = no; py = person years; † Number of people in cohort who met inclusion criteria for analysis of specified type of cancer.

Appendix C. Evidence Tables (continued)

Table C.1.1. Evidence table of the effects of omega-3 fatty acids on the risk of developing cancer in cohort studies, by cancer type.*

Cohort First Author, Year	Study Characteristics	Duration:	Eligibility criteria	Type of cancer: Ascertainment:	Applicability Funding source Quality
Netherlands Cohort Study Goldbohm, 1994[38]	Sample size† people/person-years): 3,123/NR Age (mean/range): NR/59-69 Race: NR % male: 49 # sites: 1 Location: Netherlands	Duration: 3.3 years	Inclusion: Population born between 1917 and 1931. Exclusion: Prevalent colon cancer at baseline; incomplete dietary questionnaire.	Type: colorectal Ascertainment: Regional cancer registries	Applicability: II Funding source: Unclear Quality: Adjustment for confounders: Y Blinded to exposure/outcome: NR Valid ascertainment of outcome: Y Valid ascertainment of exposure: Y Description of withdrawals and dropouts: N
New York University Women's Health Study Kato, 1997[40]	Sample size† people/person-years): 14,727/105,044 py Age (mean/range): NR/34-65 Race: Caucasian, Black, Hispanic % male: NR # sites: 2 Location: US	Duration: 7.1 years	Inclusion: Women treated at the Guttman Breast Diagnostic Institute in New York City or at the Strax Breast Cancer Institute in Florida. Exclusion: Pregnancy/Hormonal medications use.	Type: colorectal Ascertainment: Self report confirmed by medical records review supplemented by review of state cancer registries and National Death index	Applicability: III Funding source: Government Quality: Adjustment for confounders: Y Blinded to exposure/outcome: NR Valid ascertainment of outcome: Y Valid ascertainment of exposure: Y Description of withdrawals and dropouts: Y

*NR = not reported; Y = yes; N = no; py = person years; † Number of people in cohort who met inclusion criteria for analysis of specified type of cancer.

Appendix C. Evidence Tables (continued)

Table C.1.1. Evidence table of the effects of omega-3 fatty acids on the risk of developing cancer in cohort studies, by cancer type.*

Cohort First Author, Year	Study Characteristics	Duration:	Eligibility criteria	Type of cancer: Ascertainment:	Applicability Funding source Quality
Nurses' Health Study Willett, 1990[46]	Sample size† people/person-years): 88,751/510,332 py Age (mean/range): NR/30-55 Race: NR % male: NR # sites: 1 Location: US	Duration: 6 years	Inclusion: US female registered nurses born between 1921 and 1946. Exclusion: Cancer (other than non-melanoma skin cancer)/Dietary questionnaire with implausible total energy intake/Incomplete food frequency questionnaire.	Type: colorectal Ascertainment: self-report or vital records confirmed by medical records review	Applicability: II Funding source: Government Quality: Adjustment for confounders: Y Blinded to exposure/outcome: Y Valid ascertainment of outcome: Y Valid ascertainment of exposure: Y Description of withdrawals and dropouts: Y
Swedish women in mammography-screening program Terry, 2001[54]	Sample size† people/person-years): 61,463/NR Age (mean/range): NR/NR Race: NR % male: NR # sites: 1 Location: Sweden	Duration: 11 years	Inclusion: Population-based mammography screening program participants who returned a questionnaire and were free of cancer. Exclusion: NR	Type: colorectal Ascertainment: Regional cancer registries	Applicability: II Funding source: Government Quality: Adjustment for confounders: Y Blinded to exposure/outcome: NR Valid ascertainment of outcome: Y Valid ascertainment of exposure: Y Description of withdrawals and dropouts: NR

*NR = not reported; Y = yes; N = no; py = person years; † Number of people in cohort who met inclusion criteria for analysis of specified type of cancer.

Appendix C. Evidence Tables (continued)

Table C.1.1. Evidence table of the effects of omega-3 fatty acids on the risk of developing cancer in cohort studies, by cancer type.*

Cohort First Author, Year	Study Characteristics	Duration:	Eligibility criteria	Type of cancer: Ascertainment:	Applicability Funding source Quality
Lung Cancer					
Aichi Prefecture Cohort, Japan Takezaki, 2003[24]	Sample size† people/person-years): 5,885/76,928 py Age (mean/range): 57/40-79 Race: NR % male: 48 # sites: 1 Location: Japan	Duration: 14 years	Inclusion: Inhabitants in a rural area of Aichi Prefecture, Japan, born between 1917 and 1972. Exclusion: Incomplete questionnaires	Type: lung and bronchus Ascertainment: Cancer registry	Applicability: II Funding source: Unclear Quality: Adjustment for confounders: Y Blinded to exposure/outcome: NR Valid ascertainment of outcome: Y Valid ascertainment of exposure: Y Description of withdrawals and dropouts: Y
Japan Collaborative Cohort Ozasa, 2001[36]	Sample size† people/person-years): 98,248/ 796,074py Age (mean/range): NR/NR Race: Asian % male: 42 # sites: 1 Location: Japan	Duration: 9 years	Inclusion: Population of 19 prefectures in Japan born between 1909 and 1950. Exclusion: Lung cancer at baseline; non-response to survey questions about smoking.	Type: lung Ascertainment: Death certificates	Applicability: II Funding source: Government Quality: Adjustment for confounders: Y Blinded to exposure/outcome: NR Valid ascertainment of outcome: Y Valid ascertainment of exposure: Y Description of withdrawals and dropouts: Y

*NR = not reported; Y = yes; N = no; py = person years; † Number of people in cohort who met inclusion criteria for analysis of specified type of cancer.

Appendix C. Evidence Tables (continued)

Table C.1.1. Evidence table of the effects of omega-3 fatty acids on the risk of developing cancer in cohort studies, by cancer type.*

Cohort First Author, Year	Study Characteristics	Duration:	Eligibility criteria	Type of cancer: Ascertainment:	Applicability Funding source Quality
Norwegian Cohorts Kvale, 1983[56]	Sample size† people/person-years): 16,713/NR Age (mean/range): NR/NR Race: Caucasian % male: 82 # sites: NR Location: Norway	Duration: 11 years	Inclusion: Probability sample of Norway population. Male siblings living in Norway of migrants to the US; Family members, friends of subjects in case-control study of gastric cancer; "usable' dietary questionnaire. Exclusion: NR	Type: lung Ascertainment: Cancer registry	Applicability: II Funding source: Government Quality: Adjustment for confounders: Y Blinded to exposure/outcome: NR Valid ascertainment of outcome: Y Valid ascertainment of exposure: Y Description of withdrawals and dropouts: Y
Norwegian National Health Screening Service Cohort Veierod, 1997[42]	Sample size† people/person-years): 51,452/578,047 py Age (mean/range): NR/16-56 Race: NR % male: 52 # sites: 1 Location: Norway	Duration: 15 years	Inclusion: Residents of three Norwegian counties (Finnmark, Sogn og Fjordane, and Oppland) born between 1925 and 1942. Exclusion: Cancer.	Type: lung and bronchus Ascertainment: National Cancer Registry	Applicability: II Funding source: Government and private (non-industry) Quality: Adjustment for confounders: Y Blinded to exposure/outcome: NR Valid ascertainment of outcome: Y Valid ascertainment of exposure: Y Description of withdrawals and dropouts: Y

*NR = not reported; Y = yes; N = no; py = person years; † Number of people in cohort who met inclusion criteria for analysis of specified type of cancer.

Appendix C. Evidence Tables (continued)

Table C.1.1. Evidence table of the effects of omega-3 fatty acids on the risk of developing cancer in cohort studies, by cancer type.*

Cohort First Author, Year	Study Characteristics	Duration:	Eligibility criteria	Type of cancer: Ascertainment:	Applicability Funding source Quality
Lymphoma, non-Hodgkin's					
Iowa Women's Health Study Chiu, 1996[35]	Sample size† people/person-years): 35,156/233,262 py Age (mean/range): NR/55-69 Race: NR % male: NR # sites: 1 Location: US	Duration: 6 years	Inclusion: Women with valid Iowa driver's license born between 1917 and 1931. Exclusion: Prior history of cancer at any site except skin, prior use of cancer chemotherapy, incomplete questionnaire.	Type: lymphoma Ascertainment: State Health Registry of Iowa	Applicability: II Funding source: Government Quality: Adjustment for confounders: Y Blinded to exposure/outcome: NR Valid ascertainment of outcome: Y Valid ascertainment of exposure: Y Description of withdrawals and dropouts: Y
Nurses' Health Study Zhang, 1999[47]	Sample size† people/person-years): 88,410/1,169,326 py Age (mean/range): 47/34-60 Race: Caucasian, Black, Hispanic, Asian, Pacific Islander % male: NR # sites: 1 Location: US	Duration: 14 years	Inclusion: US female registered nurses born between 1921 and 1946. Exclusion: Cancer (other than non-melanoma skin cancer)/Incomplete food frequency questionnaire/Dietary questionnaire with implausible total energy intake/Missing patient characteristics information.	Type: lymphoma Ascertainment: self-report or vital records confirmed by medical records review	Applicability: II Funding source: Government Quality: Adjustment for confounders: Y Blinded to exposure/outcome: Y Valid ascertainment of outcome: Y Valid ascertainment of exposure: Y Description of withdrawals and dropouts: Y

*NR = not reported; Y = yes; N = no; py = person years; † Number of people in cohort who met inclusion criteria for analysis of specified type of cancer.

Appendix C. Evidence Tables (continued)

Table C.1.1. Evidence table of the effects of omega-3 fatty acids on the risk of developing cancer in cohort studies, by cancer type.*

Cohort First Author, Year	Study Characteristics	Duration:	Eligibility criteria	Type of cancer: Ascertainment:	Applicability Funding source Quality
Ovarian Cancer					
Nurses' Health Study Bertone, 2002[48]	Sample size† people/person-years): 80,258/NR Age (mean/range): 46/30-55 Race: NR % male: NR # sites: 1 Location: US	Duration: 15 years	Inclusion: US female registered nurses born between 1921 and 1946. Exclusion: Cancer (other than non-melanoma skin cancer)/Incomplete food frequency questionnaire/Dietary questionnaire with implausible total energy intake/Missing patient characteristics information.	Type: genital Ascertainment: self-report or vital records confirmed by medical records review	Applicability: II Funding source: Government Quality: Adjustment for confounders: Y Blinded to exposure/outcome: Y Valid ascertainment of outcome: Y Valid ascertainment of exposure: Y Description of withdrawals and dropouts: Y
Pancreatic Cancer					
Alpha-tocopherol, Beta-Carotene Cancer Prevention Study Stolzenberg-Solomon, 2002[25]	Sample size† people/person-years): 27,111/260,006 py Age (mean/range): NR/50-69 Race: NR % male: 100 # sites: 1 Location: Finland	Duration: 12 years	Inclusion: Males who smoked at least 5 cigarettes per day and that participated in a RCT of the effects of alpha-tocopherol, beta-carotene, both or placebo. Exclusion: Cancer (other than nonmelanoma skin cancer)/Angina upon exertion/Renal disease/Alcoholism/Anticoagulant use/Medical problems which limit participation/ Vitamins use.	Type: other gastrointestinal Ascertainment: Tumor registry with medical records verification	Applicability: III Funding source: Government Quality: Adjustment for confounders: Y Blinded to exposure/outcome: NR Valid ascertainment of outcome: Y Valid ascertainment of exposure: Y Description of withdrawals and dropouts: Y

*NR = not reported; Y = yes; N = no; py = person years; † Number of people in cohort who met inclusion criteria for analysis of specified type of cancer.

Appendix C. Evidence Tables (continued)

Table C.1.1. Evidence table of the effects of omega-3 fatty acids on the risk of developing cancer in cohort studies, by cancer type.*

Cohort First Author, Year	Study Characteristics	Duration:	Eligibility criteria	Type of cancer: Ascertainment:	Applicability Funding source Quality
Nurses' Health Study Michaud, 2003[49]	Sample size† people/person-years): 88,802/1,545,069 py Age (mean/range): 47/30-55 Race: Caucasian, Black, Hispanic, Asian, Pacific Islander % male: NR # sites: 1 Location: US	Duration: 18 years	Inclusion: US female registered nurses born between 1921 and 1946. Exclusion: Cancer (other than non-melanoma skin cancer)/Incomplete food frequency questionnaire/Dietary questionnaire with implausible total energy intake/Missing patient characteristics information.	Type: other gastrointestinal Ascertainment: self-report or vital records confirmed by medical records review	Applicability: II Funding source: Government Quality: Adjustment for confounders: Y Blinded to exposure/outcome: Y Valid ascertainment of outcome: Y Valid ascertainment of exposure: Y Description of withdrawals and dropouts: Y
Prostate Cancer					
Hawaii Health Surveillance Program LeMarchand, 1994[27]	Sample size† people/person-years): 8,881/NR Age (mean/range): NR/NR Race: Caucasian, Asian, Pacific Islander % male: 100 # sites: 1 Location: US	Duration: 14 years	Inclusion: Permanent residents of Hawaii. Exclusion: Previous cancer history, prostate cancer within 5 years prior to interview, missing or unreliable survey data.	Type: prostate Ascertainment: Hawaii tumor registry	Applicability: II Funding source: Government Quality: Adjustment for confounders: Y Blinded to exposure/outcome: NR Valid ascertainment of outcome: Y Valid ascertainment of exposure: Y Description of withdrawals and dropouts: Y

*NR = not reported; Y = yes; N = no; py = person years; † Number of people in cohort who met inclusion criteria for analysis of specified type of cancer.

Appendix C. Evidence Tables (continued)

Table C.1.1. Evidence table of the effects of omega-3 fatty acids on the risk of developing cancer in cohort studies, by cancer type.*

Cohort First Author, Year	Study Characteristics	Duration:	Eligibility criteria	Type of cancer: Ascertainment:	Applicability Funding source Quality
Health Professionals Follow-up Study Giovannucci, 1993[29]	Sample size† people/person-years): 47,855/166,923 py Age (mean/range): NR/40-75 Race: Caucasian, Black, Asian % male: 100 # sites: 1 Location: US	Duration: 5 years	Inclusion: Male dentists, optomotrists, oseopaths, podiatrists, pharmacists, and veterinarians that responded to a postal questionnaire born between 1911 and 1946. Exclusion: Cancer (other than nonmelanoma skin cancer)/Incomplete food frequency questionnaire.	Type: prostate Ascertainment: self-report or vital records confirmed by medical records review	Applicability: II Funding source: Government and private (non-industry) Quality: Adjustment for confounders: Y Blinded to exposure/outcome: Y Valid ascertainment of outcome: Y Valid ascertainment of exposure: Y Description of withdrawals and dropouts: Y
HealthProfessionals Follow-up Study Augustsson, 2003[28]	Sample size† people/person-years): 47,882/515,445 py Age (mean/range): NR/40-75 Race: NR % male: 100 # sites: 1 Location: US	Duration: 12 years	Inclusion: Male dentists, optomotrists, oseopaths, podiatrists, pharmacists, and veterinarians that responded to a postal questionnaire born between 1911 and 1946. Exclusion: Cancer (other than nonmelanoma skin cancer)/Incomplete food frequency questionnaire.	Type: prostate Ascertainment: self-report or vital records confirmed by medical records review	Applicability: II Funding source: Government and private (non-industry) Quality: Adjustment for confounders: Y Blinded to exposure/outcome: Y Valid ascertainment of outcome: Y Valid ascertainment of exposure: Y Description of withdrawals and dropouts: Y

*NR = not reported; Y = yes; N = no; py = person years; † Number of people in cohort who met inclusion criteria for analysis of specified type of cancer.

Appendix C. Evidence Tables (continued)

Table C.1.1. Evidence table of the effects of omega-3 fatty acids on the risk of developing cancer in cohort studies, by cancer type.*

Cohort First Author, Year	Study Characteristics	Duration:	Eligibility criteria	Type of cancer: Ascertainment:	Applicability Funding source Quality
Netherlands Cohort Study Schuurman, 1999[39]	Sample size† people/person-years): 58,279/9,123 py Age (mean/range): 63/55-69 Race: NR % male: 100 # sites: 1 Location: Netherlands	Duration: 6.3 years	Inclusion: Population born between 1917 and 1931. Exclusion: Prevalent cancer at baseline; incomplete or inconsistent dietary data.	Type: prostate Ascertainment: Regional cancer registries	Applicability: II Funding source: Government Quality: Adjustment for confounders: Y Blinded to exposure/outcome: NR Valid ascertainment of outcome: Y Valid ascertainment of exposure: Y Description of withdrawals and dropouts: Y
Seventh-day Adventist Mills, 1989[50]	Sample size† people/person-years): 14,000/66,926 py Age (mean/range): NR/NR Race: Caucasian % male: 100 # sites: 1 Location: US	Duration: 6 years	Inclusion: Seventh Day Adventist/Age 25 or older. Exclusion: Prostate cancer at baseline.	Type: prostate Ascertainment: Review of all hospital records, population based tumor registries	Applicability: III Funding source: Government Quality: Adjustment for confounders: Y Blinded to exposure/outcome: NR Valid ascertainment of outcome: Y Valid ascertainment of exposure: Y Description of withdrawals and dropouts: Y

*NR = not reported; Y = yes; N = no; py = person years; † Number of people in cohort who met inclusion criteria for analysis of specified type of cancer.

Appendix C. Evidence Tables (continued)

Table C.1.1. Evidence table of the effects of omega-3 fatty acids on the risk of developing cancer in cohort studies, by cancer type.*

Cohort First Author, Year	Study Characteristics	Duration:	Eligibility criteria	Type of cancer: Ascertainment:	Applicability Funding source Quality
Swedish Twin Registry Terry, 2001[53]	Sample size† people/person-years): 6,272/133,839 py Age (mean/range): 56/43-82 Race: NR % male: 100 # sites: 1 Location: Sweden	Duration: 30 years	Inclusion: Twins living in Sweden in 1961 born between 1886 and 1925. Exclusion: Previous cancer history; death prior to assessment.	Type: prostate Ascertainment: Cancer registry	Applicability: III Funding source: Government Quality: Adjustment for confounders: Y Blinded to exposure/outcome: NR Valid ascertainment of outcome: Y Valid ascertainment of exposure: Y Description of withdrawals and dropouts: Y
Skin Cancer					
HealthProfessionals Follow-up Study VanDam, 2000[31]	Sample size† people/person-years): 43,217/308,070 py Age (mean/range): NR/40-75 Race: Caucasian, Black, Asian % male: 100 # sites: 1 Location: US	Duration: 8 years	Inclusion: Male dentists, optomotrists, oseopaths, podiatrists, pharmacists, and veterinarians that responded to a postal questionnaire born between 1911 and 1946. Exclusion: Cancer (other than non-melanoma skin cancer)/Incomplete food frequency questionnaire.	Type: skin Ascertainment: self-report or vital records confirmed by medical records review	Applicability: II Funding source: Government and private (non-industry) Quality: Adjustment for confounders: Y Blinded to exposure/outcome: Y Valid ascertainment of outcome: Y Valid ascertainment of exposure: Y Description of withdrawals and dropouts: Y

*NR = not reported; Y = yes; N = no; py = person years; † Number of people in cohort who met inclusion criteria for analysis of specified type of cancer.

Appendix C. Evidence Tables (continued)

Table C.1.1. Evidence table of the effects of omega-3 fatty acids on the risk of developing cancer in cohort studies, by cancer type.*

Cohort First Author, Year	Study Characteristics	Duration:	Eligibility criteria	Type of cancer: Ascertainment:	Applicability Funding source Quality
Stomach Cancer					
Fukuoka Prefecture Cohort, Japan Ngoan, 2002[26]	Sample size† people/person-years): 13,000/139,390 py Age (mean/range): 59/15-96 Race: NR % male: 45 # sites: 1 Location: Japan	Duration: 14 years	Inclusion: NR Exclusion: Incomplete questionnaire	Type: other gastrointestinal Ascertainment:	Applicability: II Funding source: Government Quality: Adjustment for confounders: Y Blinded to exposure/outcome: NR Valid ascertainment of outcome: NR Valid ascertainment of exposure: Y Description of withdrawals and dropouts: NR

*NR = not reported; Y = yes; N = no; py = person years; † Number of people in cohort who met inclusion criteria for analysis of specified type of cancer.

Appendix C. Evidence Tables (continued)

Table C.1.2. Evidence table of the effects of fish consumption on the risk of developing cancer in cohort studies, by cancer type.*

Cohort First Author, Year	Study arm (quartile, quintile or dose group)	Median dose	Cases	Exposure (person-years)	Estimates of effect		
					Age adjusted RR (95% CI)	Multivariate RR (95% CI)	Multivariate Adjustors
Aerodigestive Cancer							
Honolulu Heart Program Chyou, 1995[32]	1	< 1 g/week	46	4,335	NR	1	Age ,alcohol, # of cig./d, # of yrs smoke.
	2	2-4 g/week	35	2,992	NR	1.02 (0.65, 1.61)	
	3	≥ 5 g/week	11	575	NR	1.37 (0.70, 2.69)	
						p = 0.473†	
Bladder Cancer							
Honolulu Heart Program Chyou, 1993[33]	1	≤ 1 times/week	53	NR	NR	1	Age, smoking.
	2	2-4 times/week	36	NR	NR	0.90 (0.59, 1.39)	
	3	≥ 5 times/week	7	NR	NR	0.67 (0.26, 1.67)	
						p = 0.377†	

* NR= not reported; † = test for trend.

Appendix C. Evidence Tables (continued)

Table C.1.2. Evidence table of the effects of fish consumption on the risk of developing cancer in cohort studies, by cancer type.*

Cohort First Author, Year	Study arm (quartile, quintile or dose group)	Median dose	Cases	Exposure (person-years)	Estimates of effect		
					Age adjusted RR (95% CI)	Multivariate RR (95% CI)	Multivariate Adjustors
Breast Cancer							
Diet, Cancer and Health Study Stripp, 2003[55]	1	0-26 g/day	NR	NR	1	1	Age, parity, number of births, age at first birth, BMI, benign breast tumor, years of school, use of HRT, duration of HRT use, alcohol.
	2	27-39 g/day	NR	NR	1.01 (0.77. 1.32)	0.99 (0.76, 1.30)	
	3	40-58 g/day	NR	NR	1.17 (0.89, 1.53)	1.12 (0.85, 1.47)	
	4	> 58 g/day	NR	NR	1.54 (1.18, 2.02)	1.47 (1.10, 1.98)	
	Total 23,693						
Nurses' Health Study Holmes, 2003[43]	1	≤ 0.13 servings/day	NR	NR	NR	1	Age, 2yr time period, total energy, alcohol intake, parity and age at first birth, BMI at age 18, weight change since 18, height in inches, family history of breast cancer, history of benign breast disease, age at menarche in years, menopausal status, age at menopausal and HRT use, duration of menopausal.
	2	0.14-0.20 servings/day	NR	NR	NR	0.98 (0.89, 1.08)	
	3	0.21-0.27 servings/day	NR	NR	NR	0.97 (0.87, 1.08)	
	4	0.28-0.39 servings/day	NR	NR	NR	0.99 (0.90, 1.09)	
	5	≤ 0.4 servings/day	NR	NR	NR	1.04 (0.93, 1.14)	
						p = 0.55†	

* NR= not reported; † = test for trend.

Appendix C. Evidence Tables (continued)

Table C.1.2. Evidence table of the effects of fish consumption on the risk of developing cancer in cohort studies, by cancer type.*

Cohort First Author, Year		Study arm (quartile, quintile or dose group)	Median dose	Cases	Exposure (person-years)	Estimates of effect		
						Age adjusted RR (95% CI)	Multivariate RR (95% CI)	Multivariate Adjustors
Life Span Study Key, 1999[52]	Fish (not dried)	1	≤ 1 time/week	99	125,089	NR	1	Attained age, calendar period, city, age at time of bombing and radiation dose.
		2	2-4 times/week	159	185,031	NR	1.08 (0.84, 1.39)	
		3	≥ 5 times/week	118	112,564	NR	1.17 (0.90, 1.54)	
		4	unknown	51	66,305	NR	0.92 (0.66, 1.29)	
							p = 0.21†	
	Dried fish	1	≤ 1 times/week	259	256,264	NR	1	
		2	2-4 times/week	64	81,898	NR	0.85 (0.64, 1.12)	
		3	≥ 5 times/week	7	16,264	NR	0.49 (0.24, 1.02)	
		4	unknown	97	134,563	NR	0.77 (0.60, 0.98)	
							p = 0.03†	
Norwegian National Health Screening Service Cohort Vatten, 1990[41]		1	≤ 2 times/week	103	115,470	1	NR	NR
		2	> 2 times/week	49	45,543	1.2 (0.8, 1.7)	NR NR	
						p = 0.24†		

* NR= not reported; † = test for trend.

Appendix C. Evidence Tables (continued)

Table C.1.2. Evidence table of the effects of fish consumption on the risk of developing cancer in cohort studies, by cancer type.*

Cohort First Author, Year	Study arm (quartile, quintile or dose group)	Median dose	Cases	Exposure (person-years)	Estimates of effect		
					Age adjusted RR (95% CI)	Multivariate RR (95% CI)	Multivariate Adjustors
Colorectal Cancer							
HealthProfessionals Follow-up Study Giovannucci, 1994[30]	1	8.4 g/d	41	52,817	1	NR	NR
	2	20.9 g/d	35	53,071	0.85 (0.54, 1.33)	NR	
	3	31.0 g/d	43	52,789	1.05 (0.68, 1.61)	NR	
	4	47.8 g/d	35	52,788	0.80 (0.51, 1.26)	NR	
	5	83.4 g/d	51	53,215	1.06 (0.70, 1.60)	NR	
					p = 0.79†		
Netherlands Cohort Study Goldbohm, 1994[38]	1	0 g/d	70	NR	NR	1	Age and energy.
	2	0-10 g/d	53	NR	NR	1 (0.68, 1.47)	
	3	10-20 g/d	33	NR	NR	0.74 (0.48, 1.15)	
	4	> 20 g/d	59	NR	NR	0.81 (0.56, 1.17)	
						p = 0.14†	
Nurses' Health Study Willett, 1990[46]	1	< 1 g/month	12	43,948	1	NR	NR
	2	1-3 g/month	59	173,019	1.29 (0.70, 2.40)	NR	
	3	1 g/week	54	200,732	0.92 (0.49, 1.72)	NR	
	4	2-4 g/week	19	77,277	0.75 (0.35, 1.58)	NR	
	5	4 g/week	5	15,356	1.06 (0.36, 3.12)	NR	
					p = 0.09†		

* NR= not reported; † = test for trend.

Appendix C. Evidence Tables (continued)

Table C.1.2. Evidence table of the effects of fish consumption on the risk of developing cancer in cohort studies, by cancer type.*

Cohort First Author, Year		Study arm (quartile, quintile or dose group)	Median dose	Cases	Exposure (person-years)	Estimates of effect			Multivariate Adjustors
						Age adjusted RR (95% CI)	Multivariate RR (95% CI)		
New York University Women's Health Study Kato, 1997[40]		1	NR	NR	NR	NR	1		Age, total calorie, place at enrollment and highest level of education.
		2	NR	NR	NR	NR	1.01	(0.62, 1.67)	
		3	NR	NR	NR	NR	0.65	(0.37, 1.13)	
		4	NR	NR	NR	NR	0.49	(0.27, 0.89)	
							p = 0.007†		
Lung Cancer									
Japan Collaborative Cohort Ozasa, 2001[36]	Men	1	≤ 1-2 times/week	184	150,457	NR	1‡		Age, parent's history of lung cancer, smoking status, smoking index, time since quitting smoking.
		2	3-4 times/week	112	85,300	NR	1.12	(0.87, 1.43)	
		3	Almost every day	91	69,552	NR	1.03	(0.79, 1.34)	
							p = 0.72†		
	Women	1	≤ 1-2 times/week	59	187,845	NR	1‡		
		2	3-4 times/week	24	119,381	NR	0.73	(0.45, 1.21)	
		3	Almost every day	22	95,004	NR	0.88	(0.52, 1.49)	
							p = 0.50†		
Aichi Prefecture Cohort, Japan Takezaki, 2003[24]		1	< 1 times/week	10	10,237	NR	1		Age, sex, smoke, occupation.
		2	1-2 times/week	31	33,138	NR	0.99	(0.48, 2.03)	
		3	≥ 3 times/week	10	33,551	NR	0.32	(0.13, 0.76)	
							p = 0.003†		

* NR= not reported; † = test for trend; ‡ = Hazard Ratio.

Appendix C. Evidence Tables (continued)

Table C.1.2. Evidence table of the effects of fish consumption on the risk of developing cancer in cohort studies, by cancer type.*

Cohort First Author, Year	Study arm (quartile, quintile or dose group)	Median dose	Cases	Exposure (person-years)	Estimates of effect			Multivariate Adjustors
					Age adjusted RR (95% CI)	Multivariate RR (95% CI)		
Norwegian National Health Screening Service Cohort Veierod, 1997[42]	1	< 1 times/week	9	37,979	NR	1‡		Smoking status, gender, age at inclusion, attained age.
	2	1-2 times/week	84	334,322	NR	1.1	(0.6, 2.2)	
	3	3-4 times/week	47	190,637	NR	1.0	(0.5, 2.1)	
	4	≥ 5 times/week	11	11,971	NR	3.0	(1.2, 7.3)	
						p = 0.2†		
Lymphoma, non-Hodgkin's								
Iowa Women's Health Study Chiu, 1996[35]	1	< 4 servings/ month	32	67,337	NR	1		Age and energy.
	2	4-6 servings/ month	42	91,914	NR	0.94	(0.59, 1.49)	
	3	> 6 servings/ month	30	74,011	NR	0.81	(0.49, 1.35)	
						p = 0.42†		

* NR= not reported; † = test for trend; ‡ = Incidence Rate Ratio.

Appendix C. Evidence Tables (continued)

Table C.1.2. Evidence table of the effects of fish consumption on the risk of developing cancer in cohort studies, by cancer type.*

Cohort First Author, Year	Study arm (quartile, quintile or dose group)	Median dose	Cases	Exposure (person-years)	Estimates of effect		
					Age adjusted RR (95% CI)	Multivariate RR (95% CI)	Multivariate Adjustors
Pancreatic Cancer							
Alpha-tocopherol, Beta-Carotene Cancer Prevention Study Stolzenberg-Solomon, 2002[25]	1	NR	NR	NR	NR	1	Energy intake by the residual method, age, and years of smoking, energy-adjusted saturated fat intake.
	2	NR	NR	NR	NR	1.22 (0.75, 1.97)	
	3	NR	NR	NR	NR	1.14 (0.70, 1.86)	
	4	NR	NR	NR	NR	1.07 (0.65, 1.76)	
	5	NR	NR	NR	NR	0.91 (0.54, 1.52)	
						p = 0.59†	
Prostate Cancer							
Health Professionals Follow-up Study Augustsson, 2003[28]	1	< 2 g/month	320	73,601	1	1	Age, calories, fatty acid, lycopene, retinol, vitamin D and physical activity.
	2	2 g/month-1 g/week	487	99,162	1.06 (0.92, 1.22)	1.05 (0.91, 1.21)	
	3	2-3 g/week	1,181	232,606	1.06 (0.94, 1.20)	1.06 (0.93, 1.20)	
	4	> 3 g/week	494	110,076	0.91 (0.79, 1.05)	0.93 (0.80, 1.08)	
Hawaii Health Surveillance Program LeMarchand, 1994[27]	1	NR	NR	NR	NR	1	Age, race, income.
	2	NR	NR	NR	NR	1.1 (0.7, 1.7)	
	3	NR	NR	NR	NR	0.9 (0.6, 1.3)	
	4	NR	NR	NR	NR	1.2 (0.8, 1.8)	
						p = 0.55†	

* NR= not reported; † = test for trend.

Appendix C. Evidence Tables (continued)

Table C.1.2. Evidence table of the effects of fish consumption on the risk of developing cancer in cohort studies, by cancer type.*

Cohort First Author, Year	Study arm (quartile, quintile or dose group)	Median dose	Cases	Exposure (person-years)	Estimates of effect		
					Age adjusted RR (95% CI)	Multivariate RR (95% CI)	Multivariate Adjustors
Seventh-day Adventist Mills, 1989[50]	1	Never	43	24,916	1	NR	NR
	2	< 1 g/week	86	34,413	1.68 (1.16, 2.43)	NR	
	3	≥ 1 g/week	17	7,597	1.47 (0.84, 2.60)	NR	
					p = 0.03†		
Swedish Twin Registry Terry, 2001[53]	1	Never/ seldom	14	2,406	1.7 (1.0, 3.0)	2.3 (1.2, 4.5)	Age, BMI, physical activity, smoking, consumption of alcohol, red meat, processed meat, fruit, vegetable and milk.
	2	Small	201	55,753	1.1 (0.9, 1.3)	1.2 (1.0, 1.4)	
	3	Moderate	209	64,458	1	1	
	4	Large	42	11,222	1.1 (0.8, 1.5)	1.0 (0.7, 1.6)	
					p = 0.35†	p = 0.05†	

* NR= not reported; † = test for trend.

Appendix C. Evidence Tables (continued)

Table C.1.2. Evidence table of the effects of fish consumption on the risk of developing cancer in cohort studies, by cancer type.*

Cohort First Author, Year	Study arm (quartile, quintile or dose group)	Median dose	Cases	Exposure (person-years)	Estimates of effect		
					Age adjusted RR (95% CI)	Multivariate RR (95% CI)	Multivariate Adjustors
Stomach Cancer							
Fukuoka Prefecture Cohort, Japan Ngoan, 2002[26]	1	Low	19	2,366	NR	1	Age, sex, smoking, processed meat, liver, cooking or salad oil, suimono and pickled food.
	2	Medium	58	7,219	NR	1.1 (0.5, 2.3)	
	3	High	30	2,780	NR	1.0 (0.4, 2.2)	
Stomach cancer including first 3 years follow-up						p = 0.05†	
Fukuoka Prefecture Cohort, Japan Ngoan, 2002[26]	1	Low	19	2,366	NR	1	
	2	Medium	58	7,219	NR	0.9 (0.4, 2.2)	
	3	High	30	2,780	NR	0.9 (0.3, 2.1)	
Stomach cancer excluding first 3 years follow-up						p = 0.05†	

* NR= not reported; † = test for trend.

Appendix C. Evidence Tables (continued)

Table C.1.3. Evidence table of the effects of omega-3 consumption on the risk of developing cancer in cohort studies, by cancer type.*

Cohort First Author, Year	Study arm (quartile, quintile or dose group)	Median dose	Cases	Exposure (person-years)	Estimates of effect		
					Age adjusted RR (95% CI)	Multivariate RR (95% CI)	Multivariate Adjustors
Breast Cancer							
Singapore Chinese Health Study Gago-Dominguez, 2003[51]	1	NR	88	NR	NR	1	Age at baseline interview, year of recruitment, dialect group, education, daily alcohol drinker, family history of breast cancer, age when period became regular, number of live births.
	2	NR	73	NR	NR	0.82 (0.60, 1.12)	
	3	NR	74	NR	NR	0.84 (0.62, 1.15)	
	4	NR	79	NR	NR	0.87 (0.64, 1.18)	
						p = 0.40†	
Colorectal Cancer							
Iowa Women's Health Study Bostick, 1994[34]	1	< 0.03 g/d	62	NR	1	1	Age, total energy intake, height, parity, total vitamin E, a total vitamin E by age interaction term, vitamin A supplement intake.
	2	0.03-0.05 g/d	46	NR	0.67 NR	0.82 (0.55, 1.24)	
	3	0.06-0.10 g/d	28	NR	0.61 NR	0.77 (0.50, 1.17)	
	4	0.11-0.18 g/d	44	NR	0.72 NR	0.96 (0.64, 1.43)	
	5	> 0.18 g/d	32	NR	0.60 NR	0.70 (0.45, 1.09)	
					p = 0.04†	p = 0.26†	

* NR = not reported; † = test for trend.

Appendix C. Evidence Tables (continued)

Table C.1.3. Evidence table of the effects of omega-3 consumption on the risk of developing cancer in cohort studies, by cancer type.*

Cohort First Author, Year	Study arm (quartile, quintile or dose group)	Median dose	Cases	Exposure (person-years)	Estimates of effect		
					Age adjusted RR (95% CI)	Multivariate RR (95% CI)	Multivariate Adjustors
Lymphoma, non-Hodgkin's							
Nurses' Health Study Zhang, 1999[47]	1	0.02 % of energy intake	33	NR	1	1	Age, total energy, length of follow-up, geographic region, cigarette smoke, height in inches, saturated and trans unsaturated fats, fruit, vegetable intake.
	2	0.03 % of energy intake	40	NR	1.2 NR	1.2 NR	
	3	0.04 % of energy intake	46	NR	1.3 NR	1.4 NR	
	4	0.05 % of energy intake	39	NR	1.1 NR	1.2 NR	
	5	0.10 % of energy intake	41	NR	1.1 (0.7, 1.7)	1.4 (0.8, 2.2)	
					p = 0.90†	NR	
Pancreatic Cancer							
Alpha-tocopherol, Beta-Carotene Cancer Prevention Study Stolzenberg-Solomon, 2002[25]	1	NR	NR	NR	NR	1	Energy intake by the residual method, age, and years of smoking.
	2	NR	NR	NR	NR	0.97 (0.60, 1.60)	
	3	NR	NR	NR	NR	1.04 (0.64, 1.69)	
	4	NR	NR	NR	NR	1.16 (0.72, 1.86)	
	5	NR	NR	NR	NR	0.96 (0.58, 1.58)	
						p = 0.90†	

* NR = not reported; † = test for trend.

Appendix C. Evidence Tables (continued)

Table C.1.3. Evidence table of the effects of omega-3 consumption on the risk of developing cancer in cohort studies, by cancer type.*

Cohort First Author, Year	Study arm (quartile, quintile or dose group)	Median dose	Cases	Exposure (person-years)	Estimates of effect		
					Age adjusted RR (95% CI)	Multivariate RR (95% CI)	Multivariate Adjustors
Prostate Cancer							
HealthProfessionals Follow-up Study Giovannucci, 1993[29]	1	0.05 g/d	22	32,290	1	NR	NR
	2	0.12 g/d	32	35,643	1.34 (0.78, 2.30)	NR	
	3	0.21 g/d	24	30,807	1.05 (0.59, 1.89)	NR	
	4	0.30 g/d	24	35,639	0.92 (0.51, 1.65)	NR	
	5	0.55 g/d	24	32,787	0.90 (0.51, 1.61)	NR	
					p = 0.30†		
Skin, BCC							
HealthProfessionals Follow-up Study VanDam, 2000[31]	1	0.07 g/d	604	63,581	1	1	Age, 2-year follow-up period, major ancestry, energy intake, BMI, hair color, frequency of routine physical examinations, cigarette smoking, mean annual solar radiation in region of residence, fat.
	2	0.15 g/d	590	62,641	0.98 NR	0.97 (0.86, 1.09)	
	3	0.24 g/d	644	61,641	1.07 NR	1.04 (0.93, 1.17)	
	4	0.34 g/d	642	60,495	1.07 NR	1.05 (0.93, 1.18)	
	5	0.58 g/d	710	59,712	1.14 NR	1.13 (1.01, 1.27)	
					p = 0.003†	p = 0.008†	

* NR = not reported; † = test for trend.

Appendix C. Evidence Tables (continued)

Table C.1.4. Evidence table of the effects of alpha-linolenic acid consumption on the risk of developing cancer in cohort studies, by cancer type.*

Cohort First Author, Year	Study arm (quartile, quintile, or dose group)	Median dose	Cases	Exposure (person-years)	Estimates of effect		
					Age adjusted RR (95% CI)	Multivariate RR (95% CI)	Multivariate Adjustors
Breast Cancer							
Netherlands Cohort Study Voorips, 2002[37]	1	0.6 g/d	194	NR	1	1	Age, history of benign breast cancer, breast cancer in one or more sisters, age at menarche, age at menopause, oral contraceptive use, parity, age at first childbirth, Quetelet index, education, alcohol use, current cigarette smoking, total energy intake, total energy-adjusted fat intake.
	2	0.8 g/d	145	NR	0.76 (0.58, 1.00)	0.78 (0.57, 1.05)	
	3	1.0 g/d	187	NR	0.92 (0.71, 1.20)	1.03 (0.76, 1.39)	
	4	1.3 g/d	133	NR	0.69 (0.52, 0.91)	0.74 (0.54, 1.00)	
	5	1.7 g/d	124	NR	0.68 (0.51, 0.91)	0.70 (0.51, 0.97)	
					p = 0.001†	p = 0.006†	

* NR = not reported; † = test for trend.

Appendix C. Evidence Tables (continued)

Table C.1.4. Evidence table of the effects of alpha-linolenic acid consumption on the risk of developing cancer in cohort studies, by cancer type.*

Cohort First Author, Year	Study arm (quartile, quintile, or dose group)	Median dose	Cases	Exposure (person-years)	Estimates of effect		
					Age adjusted RR (95% CI)	Multivariate RR (95% CI)	Multivariate Adjustors
Colorectal Cancer							
Swedish women in mammography-screening program Terry, 2001[54]	1	0.45 g/d	NR	NR	NR	1	Age, BMI, education level, energy intake, intakes of red meat and alcohol, energy, dietary fiber, calcium, vitamin C, folic acid, Vitamin D, saturated fat, monounsaturated fat, polyunsaturated fat.
	2	0.50 g/d	NR	NR	NR	0.96 (0.68, 1.35)	
	3	0.54 g/d	NR	NR	NR	0.96 (0.67, 1.37)	
	4	0.70 g/d	NR	NR	NR	0.90 (0.63, 1.28)	
						p = 0.57†	
	1	0.45 g/d	NR	NR	NR	1	
	2	0.50 g/d	NR	NR	NR	0.96 (0.73, 1.27)	
	3	0.54 g/d	NR	NR	NR	0.96 (0.72, 1.28)	
	4	0.70 g/d	NR	NR	NR	0.99 (0.75, 1.32)	
						p = 0.99†	
	1	0.45 g/d	NR	NR	NR	1	
	2	0.50 g/d	NR	NR	NR	0.95 (0.60, 1.52)	
	3	0.54 g/d	NR	NR	NR	0.92 (0.56, 1.49)	
	4	0.70 g/d	NR	NR	NR	1.11 (0.70, 1.78)	

* NR = not reported; † = test for trend.

Appendix C. Evidence Tables (continued)

Table C.1.4. Evidence table of the effects of alpha-linolenic acid consumption on the risk of developing cancer in cohort studies, by cancer type.*

Cohort First Author, Year	Study arm (quartile, quintile, or dose group)	Median dose	Cases	Exposure (person-years)	Estimates of effect		
					Age adjusted RR (95% CI)	Multivariate RR (95% CI)	Multivariate Adjustors
Ovarian Cancer							
Nurses' Health Study Bertone, 2002[48]	1	NR	71	NR	1.0	1.0	Age, parity, age at menarche, oral contraceptive use and duration, menopausal status/postmenopausal hormone use, smoking status.
	2	NR	52	NR	0.74 NR	0.95 (0.68, 1.33)	
	3	NR	45	NR	0.62 NR	0.80 (0.56, 1.14)	
	4	NR	62	NR	0.86 NR	0.82 (0.58, 1.15)	
	5	NR	71	NR	0.98 NR	0.88 (0.62, 1.24)	
						p = 0.27†	
Pancreatic Cancer							
Nurses' Health Study Michaud, 2003[49]	1	0.7 g/d	42	303,896	1	1	Pack-years of smoking, BMI, history of diabetes mellitus, caloric intake, height, physical activity, menopausal status, glycemic load intake.
	2	0.8 g/d	40	304,791	1.03 NR	1.08 (0.70, 1.67)	
	3	0.9 g/d	39	315,822	1 NR	1.03 (0.66, 1.61)	
	4	1.0 g/d	29	318,512	0.75 NR	0.80 (0.49, 1.30)	
	5	1.1 g/d	28	302,048	0.76 NR	0.77 (0.47, 1.26)	
					p = 0.12†	p = 0.16†	
Alpha-tocopherol, Beta-Carotene Cancer Prevention Study Stolzenberg-Solomon, 2002[25]	1	NR	NR	NR	NR	1	Energy intake by the residual method, age, and years of smoking, energy-adjusted saturated fat intake.
	2	NR	NR	NR	NR	1.09 (0.69, 1.73)	
	3	NR	NR	NR	NR	1.10 (0.68, 1.79)	
	4	NR	NR	NR	NR	1.04 (0.61, 1.77)	
	5	NR	NR	NR	NR	1.11 (0.65, 1.91)	
						p = 0.77†	

* NR = not reported; † = test for trend.

Appendix C. Evidence Tables (continued)

Table C.1.4. Evidence table of the effects of alpha-linolenic acid consumption on the risk of developing cancer in cohort studies, by cancer type.*

Cohort First Author, Year	Study arm (quartile, quintile, or dose group)	Median dose	Cases	Exposure (person-years)	Estimates of effect		
					Age adjusted RR (95% CI)	Multivariate RR (95% CI)	Multivariate Adjustors
Prostate Cancer							
Health Professionals Follow-up Study Leitzmann, 2004[57] Prostate cancer excluding stage A-1	1	<0.37% of energy	300	NR	1.0	1.0	Age, time period, major ancestry, family history of prostate cancer, BMI at age 21, height, type 2 diabetes, vasectomy, cigarettes in past decade, vigorous physical activity, intake of total energy, % energy from protein, % energy from monounsaturated fat, % energy from saturated fat, % energy from *trans* unsaturated fats, and intakes of calcium, supplemental vitamin E and lycopene.
	2	0.37-0.43% of energy	349	NR	1.08 NR	1.04 (0.89, 1.22)	
	3	0.44-0.49% of energy	354	NR	1.12 NR	1.05 (0.89, 1.25)	
	4	0.50-0.58% of energy	379	NR	1.24 NR	1.16 (0.97, 1.39)	
	5	>0.58% of energy	297	NR	1.11 NR	1.04 (0.85, 1.27)	
					p = 0.10†	p = 0.54†	
Health Professionals Follow-up Study Leitzmann, 2004[57] Advanced prostate cancer	1	<0.37% of energy	82	NR	1.0	1.0	
	2	0.37-0.43% of energy	89	NR	1.33 NR	1.47 (1.07, 2.01)	
	3	0.44-0.49% of energy	87	NR	1.41 NR	1.57 (1.12, 2.21)	
	4	0.50-0.58% of energy	90	NR	1.53 NR	1.77 (1.24, 2.53)	
	5	>0.58% of energy	100	NR	1.69 NR	1.98 (1.34, 2.93)	
					p = 0.0005†	p = 0.001†	

* NR = not reported; † = test for trend.

Appendix C. Evidence Tables (continued)

Table C.1.4. Evidence table of the effects of alpha-linolenic acid consumption on the risk of developing cancer in cohort studies, by cancer type.*

Cohort First Author, Year	Study arm (quartile, quintile, or dose group)	Median dose	Cases	Exposure (person-years)	Estimates of effect		
					Age adjusted RR (95% CI)	Multivariate RR (95% CI)	Multivariate Adjustors
Netherlands Cohort Study Schuurman, 1999[39]	1	0.7 g/d	154	1,802	1	1	Age, family history of prostate carcinoma, socioeconomic status, total energy intake, total energy-adjusted fat intake.
	2	1.1 g/d	126	1,820	0.80 (0.59, 1..08)	0.76 (0.55, 1.05)	
	3	1.3 g/d	125	1,808	0.82 (0.61, 1.11)	0.82 (0.60, 1.13)	
	4	1.7 g/d	123	1,838	0.80 (0.59, 1.08)	0.80 (0.59, 1.10)	
	5	2.1 g/d	114	1,855	0.76 (0.56, 1.03)	0.76 (0.66, 1.04)	
					p = 0.04	p = 0.09	

* NR = not reported; † = test for trend.

Appendix C. Evidence Tables (continued)

Table C.1.5. Evidence table of the effects of EPA consumption on the risk of developing cancer in cohort studies, by cancer type.*

Cohort First Author, Year	Study arm (quartile, quintile or dose group)	Median dose	Cases	Exposure (person-years)	Estimates of effect		
					Age adjusted RR (95% CI)	Multivariate RR (95% CI)	Multivariate Adjustors
Breast Cancer							
Netherlands Cohort Study Voorips, 2002[37]	1	0 g/d	152	NR	1	1	Age, history of benign breast cancer, breast cancer in one or more sisters, age at menarche, age at menopause, oral contraceptive use, parity, age at first childbirth, Quetelet index, education, alcohol use, current cigarette smoking, total energy intake, total energy-adjusted fat intake.
	2	0.01 g/d	145	NR	1.18 (0.88, 1.56)	1.15 (0.84, 1.58)	
	3	0.02 g/d	170	NR	1.14 (0.87, 1.50)	1.10 (0.82, 1.49)	
	4	0.04 g/d	172	NR	1.23 (0.93, 1.62)	1.22 (0.90, 1.65)	
	5	0.08 g/d	144	NR	1.03 (0.78, 1.37)	0.98 (0.72, 1.35)	
					p = 0.63†	p = 0.87†	

* NR = not reported; † = test for trend.

Appendix C. Evidence Tables (continued)

Table C.1.5. Evidence table of the effects of EPA consumption on the risk of developing cancer in cohort studies, by cancer type.*

Cohort First Author, Year	Study arm (quartile, quintile or dose group)	Median dose	Cases	Exposure (person-years)	Estimates of effect		
					Age adjusted RR (95% CI)	Multivariate RR (95% CI)	Multivariate Adjustors
Colorectal Cancer							
Swedish women in mammography-screening program Terry, 2001[54]	1	0.03 g/d	NR	NR	NR	1	Age, BMI, education level, energy intake, intakes of red meat and alcohol, energy, dietary fiber, calcium, vitamin C, folic acid, Vitamin D, saturated fat, monounsaturated fat, polyunsaturated fat.
	2	0.05 g/d	NR	NR	NR	0.76 (0.54, 1.06)	
	3	0.07 g/d	NR	NR	NR	0.81 (0.58, 1.15)	
	4	0.09 g/d	NR	NR	NR	0.85 (0.60, 1.21)	
						p = 0.46†	
	1	0.03 g/d	NR	NR	NR	1	
	2	0.05 g/d	NR	NR	NR	0.80 (0.68, 1.15)	
	3	0.07 g/d	NR	NR	NR	0.96 (0.73, 1.26)	
	4	0.09 g/d	NR	NR	NR	0.96 (0.72, 1.28)	
						p = 0.91†	
	1	0.03 g/d	NR	NR	NR	1	
	2	0.05 g/d	NR	NR	NR	1.17 (0.75, 1.83)	
	3	0.07 g/d	NR	NR	NR	1.29 (0.80, 2.06)	
	4	0.09 g/d	NR	NR	NR	1.25 (0.75, 2.06)	
						p = 0.35†	
Ovarian Cancer							
Nurses' Health Study Bertone, 2002[48]	1	NR	45	NR	1	1	Age, parity, age at menarche, oral contraceptive use and duration, menopausal status/postmenopausal hormone use, smoking status.
	2	NR	40	NR	1.01 NR	1.04 (0.68, 1.59)	
	3	NR	32	NR	0.73 NR	0.75 (0.47, 1.17)	
	4	NR	43	NR	0.96 NR	1.00 (0.66, 1.52)	
	5	NR	43	NR	0.96 NR	0.97 (0.64, 1.48)	
						p = 0.80†	

* NR = not reported; † = test for trend.

Table C.1.5. Evidence table of the effects of EPA consumption on the risk of developing cancer in cohort studies, by cancer type.*

Cohort First Author, Year	Study arm (quartile, quintile or dose group)	Median dose	Cases	Exposure (person-years)	Estimates of effect		
					Age adjusted RR (95% CI)	Multivariate RR (95% CI)	Multivariate Adjustors
Prostate Cancer							
Health Professionals Follow-up Study Leitzmann, 2004[57] Prostate cancer excluding stage A-1	1	<0.014% of energy	282	NR	1.0	1.0	Age, time period, major ancestry, family history of prostate cancer, BMI at age 21, height, type 2 diabetes, vasectomy, cigarettes in past decade, vigorous physical activity, intake of total energy, % energy from protein, % energy from monounsaturated fat, % energy from saturated fat, % energy from *trans* unsaturated fats, and intakes of calcium, supplemental vitamin E and lycopene.
	2	0.014-0.027% of energy	353	NR	1.14 NR	1.09 (0.93, 1.28)	
	3	0.028-0.042% of energy	347	NR	1.06 NR	1.02 (0.87, 1.21)	
	4	0.043-0.066% of energy	343	NR	1.03 NR	0.97 (0.81, 1.15)	
	5	>0.066% of energy	354	NR	0.92 NR	0.87 (0.72, 1.06)	
					p = 0.04†	p = 0.03†	
Health Professionals Follow-up Study Leitzmann, 2004[57] Advanced prostate cancer	1	<0.014% of energy	87	NR	1.0	1.0	
	2	0.014-0.027% of energy	92	NR	1.01 NR	1.05 (0.75, 1.37)	
	3	0.028-0.042% of energy	94	NR	1.03 NR	0.99 (0.73, 1.35)	
	4	0.043-0.066% of energy	86	NR	0.89 NR	0.87 (0.63, 1.21)	
	5	>0.066% of energy	89	NR	0.82 NR	0.82 (0.58, 1.17)	
					p = 0.08†	p = 0.18†	
Netherlands Cohort Study Schuurman, 1999[39]	1	0 g/d	135	1,918	1	1	Age, family history of prostate carcinoma, socioeconomic status, total energy intake, total energy-adjusted fat intake.
	2	0.01 g/d	102	1,853	0.69 (0.50, 0.95)	0.66 (0.47, 0.91)	
	3	0.03 g/d	125	1,790	0.94 (0.69, 1.28)	0.92 (0.67, 1.27)	
	4	0.05 g/d	138	1,771	1.06 (0.79, 1.46)	1.05 (0.77, 1.44)	
	5	0.10 g/d	142	1,790	1.01 (0.75, 1.37)	1.00 (0.73, 1.35)	
					p = 0.11†	p = 0.10†	

* NR = not reported; † = test for trend.

Appendix C. Evidence Tables (continued)

Table C.1.6. Evidence table of the effects of DHA consumption on the risk of developing cancer in cohort studies, by cancer type.*

Cohort First Author, Year	Study arm (quartile, quintile or dose group)	Median dose	Cases	Exposure (person-years)	Estimates of effect		
					Age adjusted RR (95% CI)	Multivariate RR (95% CI)	Multivariate Adjustors
Breast Cancer							
Netherlands Cohort Study Voorips, 2002[37]	1	0.01 g/d	147	NR	1	1	Age, history of benign breast cancer, breast cancer in one or more sisters, age at menarche, age at menopause, oral contraceptive use, parity, age at first childbirth, Quetelet index, education, alcohol use, current cigarette smoking, total energy intake, total energy-adjusted fat intake.
	2	0.03 g/d	156	NR	1.11 (0.83, 1.47)	1.10 (0.81, 1.51)	
	3	0.05 g/d	158	NR	1.04 (0.78, 1.37)	1.03 (0.76, 1.40)	
	4	0.08 g/d	176	NR	1.20 (0.91, 1.58)	1.21 (0.90, 1.64)	
	5	0.14 g/d	146	NR	1.02 (0.77, 1.36)	1.00 (0.72, 1.37)	
					p = 0.62†	p = 0.70†	

* NR = not reported; † = test for trend.

Appendix C. Evidence Tables (continued)

Table C.1.6. Evidence table of the effects of DHA consumption on the risk of developing cancer in cohort studies, by cancer type.*

Cohort First Author, Year	Study arm (quartile, quintile or dose group)	Median dose	Cases	Exposure (person-years)	Estimates of effect		
					Age adjusted RR (95% CI)	Multivariate RR (95% CI)	Multivariate Adjustors
Colorectal Cancer							
Swedish women in mammography-screening program Terry, 2001[54]	1	0.08 g/d	NR	NR	NR	1	Age, BMI, education level, energy intake, intakes of red meat and alcohol, energy, dietary fiber, calcium, vitamin C, folic acid, Vitamin D, saturated fat, monounsaturated fat, polyunsaturated fat.
	2	0.11 g/d	NR	NR	NR	0.84 (0.60, 1.17)	
	3	0.13 g/d	NR	NR	NR	0.74 (0.51, 1.06)	
	4	0.18 g/d	NR	NR	NR	0.88 (0.61, 1.26)	
						p = 0.41†	
	1	0.08 g/d	NR	NR	NR	1	
	2	0.11 g/d	NR	NR	NR	0.88 (0.67, 1.15)	
	3	0.13 g/d	NR	NR	NR	0.87 (0.66, 1.15)	
	4	0.18 g/d	NR	NR	NR	0.90 (0.67, 1.20)	
						p = 0.49†	
	1	0.08 g/d	NR	NR	NR	1	
	2	0.11 g/d	NR	NR	NR	1.03 (0.66, 1.61)	
	3	0.13 g/d	NR	NR	NR	1.16 (0.73, 1.84)	
	4	0.18 g/d	NR	NR	NR	1.03 (0.62, 1.71)	
						p = 0.79†	
Ovarian Cancer							
Nurses' Health Study Bertone, 2002[48]	1	NR	43	NR	1	1	Age, parity, age at menarche, oral contraceptive use and duration, menopausal status/postmenopausal hormone use, smoking status.
	2	NR	46	NR	1.06 NR	1.06 (0.70, 1.61)	
	3	NR	28	NR	0.67 NR	0.67 (0.42, 1.08)	
	4	NR	47	NR	1.05 NR	1.07 (0.71, 1.63)	
	5	NR	39	NR	0.88 NR	0.86 (0.55, 1.33)	
						p = 0.52†	

* NR = not reported; † = test for trend.

Appendix C. Evidence Tables (continued)

Table C.1.6. Evidence table of the effects of DHA consumption on the risk of developing cancer in cohort studies, by cancer type.*

Cohort First Author, Year	Study arm (quartile, quintile or dose group)	Median dose	Cases	Exposure (person-years)	Estimates of effect		
					Age adjusted RR (95% CI)	Multivariate RR (95% CI)	Multivariate Adjustors
Prostate Cancer							
Health Professionals Follow-up Study Leitzmann, 2004[57] Prostate cancer excluding stage A-1	1	<0.032% of energy	273	NR	1.0	1.0	Age, time period, major ancestry, family history of prostate cancer, BMI at age 21, height, type 2 diabetes, vasectomy, cigarettes in past decade, vigorous physical activity, intake of total energy, % energy from protein, % energy from monounsaturated fat, % energy from saturated fat, % energy from *trans* unsaturated fats, and intakes of calcium, supplemental vitamin E and lycopene.
	2	0.032-0.053% of energy	349	NR	1.16 NR	1.13 (0.96, 1.33)	
	3	0.054-0.079% of energy	333	NR	1.03 NR	0.99 (0.83, 1.17)	
	4	0.080-0.122% of energy	350	NR	1.03 NR	0.99 (0.83, 1.19)	
	5	>0.122% of energy	374	NR	1.03 NR	1.02 (0.84, 1.25)	
					p = 0.63†	p = 0.77†	
Health Professionals Follow-up Study Leitzmann, 2004[57] Advanced prostate cancer	1	<0.032% of energy	94	NR	1.0	1.0	
	2	0.032-0.053% of energy	82	NR	0.84 NR	0.79 (0.58, 1.07)	
	3	0.054-0.079% of energy	94	NR	0.91 NR	0.84 (0.62, 1.15)	
	4	0.080-0.122% of energy	89	NR	0.86 NR	0.82 (0.59, 1.13)	
	5	>0.122% of energy	89	NR	0.73 NR	0.71 (0.49, 1.08)	
					p = 0.06†	p = 0.13†	
Netherlands Cohort Study Schuurman, 1999[39]	1	0.01 g/d	124	1,846	1	1	Age, family history of prostate carcinoma, socioeconomic status, total energy intake, total energy-adjusted fat intake.
	2	0.03 g/d	111	1,834	0.82 (0.60, 1.13)	0.81 (0.58, 1.11)	
	3	0.06 g/d	128	1,811	1.01 (0.74, 1.38)	1.00 (0.73, 1.38)	
	4	0.09 g/d	139	1,836	1.07 (0.79, 1.46)	1.09 (0.80, 1.49)	
	5	0.18 g/d	140	1,796	1.05 (0.77, 1.42)	1.03 (0.75, 1.40)	
					p = 0.19†	p = 0.19†	

* NR = not reported; † = test for trend.

Appendix C. Evidence Tables (continued)

Table C.2.1. Evidence table of clinical trials of the clinical effects of omega-3 fatty acids on clinical outcomes after cancer treatment.*

First Author, Year	Study Characteristics	Study Design Duration	Eligibility criteria	Cancer treatment	Arm	Interventions Dosage/Duration
Braga, 2002[64]	Sample size: 200 Age (mean/range): 62/18-99 Race: NR % male: 59 # sites: 1 Location: Italy	Design: RCT Duration: 8 days	Inclusion: Histologically proven GI neoplasm/Undergoing abdominal surgery/Age=18 Exclusion: Evidence of infection/Renal disease/Impaired liver function/Pulmonary dysfunction/Vegetarianism/Pregnancy	Surgery	1	Standard hospital diet 1.0 liter/variable days
					2	Isoenergetic control diet 1.0 liter/variable days
					3	N3 fatty acids, Arginine 1.0 liter/variable days
					4	N3 fatty acids, Arginine 1.0 liter/variable days
Braga, 2002[65]	Sample size: 150 Age (mean/range): 65/NR Race: NR % male: 56 # sites: 1 Location: Italy	Design: RCT Duration: Variable	Inclusion: Undergoing abdominal surgery/Weight loss/Histologically proven GI neoplasm Exclusion: Evidence of infection/Pregnancy/Impaired liver function/Pulmonary dysfunction/Karnofsky score < 60/Cardiac dysfunction/Immune disorders	Surgery	1	Enteral standard diet, Standard hospital diet plus N6 polyunsaturated fat
					2	Enteral standard diet plus N6 polyunsaturated fat
					3	Enteral standard diet, N3 fatty acids plus N6 polyunsaturated fat

* NR = Not Reported.

Appendix C. Evidence Tables (continued)

Table C.2.1. Evidence table of clinical trials of the clinical effects of omega-3 fatty acids on clinical outcomes after cancer treatment.*

First Author, Year	Study Characteristics	Study Design Duration	Eligibility criteria	Cancer treatment	Arm	Interventions Dosage/Duration
Braga, 1995[66]	Sample size: 77 Age (mean/range): 6/NR Race: NR % male: NR # sites: 1 Location: Italy	Design: RCT Duration: 11 days	Inclusion: Upper gastrointestinal malignancies/Undergoing abdominal surgery Exclusion: NR	Surgery	1	Isocaloric TPN variable dose
					2	Omega6 fatty acids variable dose
					3	N3 fatty acids, Arginine variable dose
Braga, 1999[67]	Sample size: 171 Age (mean/range): 61/18-75 Race: NR % male: 62 # sites: 1 Location: Italy	Design: RCT Duration: 7 days	Inclusion: Undergoing abdominal surgery/Colorectal cancer/Upper gastrointestinal malignancies Exclusion: Impaired liver function/Pulmonary dysfunction/Cardiac dysfunction/Renal disease/Immunosuppressive medications use/Radiation therapy/Immune disorders/Evidence of infection	Surgery	1	Isoenergetic control diet 1.0 Liter/day
					2	Fish oil, Arginine 1.0 Liter/day

* NR = Not Reported.

Appendix C. Evidence Tables (continued)

Table C.2.1. Evidence table of clinical trials of the clinical effects of omega-3 fatty acids on clinical outcomes after cancer treatment.*

First Author, Year	Study Characteristics	Study Design Duration	Eligibility criteria	Cancer treatment	Arm	Interventions Dosage/Duration
Daly, 1992[68]	Sample size: 85 Age (mean/range): 63/NR Race: NR % male: 64 # sites: 1 Location: US	Design: RCT Duration: 7 days	Inclusion: Upper gastrointestinal malignancies/Undergoing abdominal surgery/Normal renal function/Normal hepatic function Exclusion: History benign intestinal disease/Previous abdominal or pelvic radiotherapy/Evidence of infection/Steroids use	Surgery	1	Enteral standard diet variable dose plus Linoleic acid
					2	EPA + DHA variable dose plus Linoleic acid
Daly, 1995[69]	Sample size: 60 Age (mean/range): 61/NR Race: NR % male: 68 # sites: 1 Location: US	Design: RCT Duration: Variable	Inclusion: Upper gastrointestinal malignancies/Undergoing abdominal surgery/Normal renal function/Normal hepatic function Exclusion: History benign intestinal disease/Previous abdominal or pelvic radiotherapy/Evidence of infection/Steroids use	Surgery, chemotherapy, and radiation	1	Enteral standard diet variable dose
					2	Enteral standard diet variable dose
					3	EPA + DHA variable dose plus Linoleic acid
					4	EPA + DHA variable dose plus Linoleic acid
Di Carlo, 1999[70]	Sample size: 100 Age (mean/range): 62/NR Race: NR % male: 62 # sites: 1 Location: Italy	Design: RCT Duration: Variable	Inclusion: Undergoing abdominal surgery Exclusion: NR	Surgery	1	Standard enteral formula variable dose
					2	Standard TPN variable dose
					3	N3 fatty acids, Arginine variable dose

* NR = Not Reported.

Appendix C. Evidence Tables (continued)

Table C.2.1. Evidence table of clinical trials of the clinical effects of omega-3 fatty acids on clinical outcomes after cancer treatment.*

First Author, Year	Study Characteristics	Study Design Duration	Eligibility criteria	Cancer treatment	Arm	Interventions Dosage/Duration
Fearon, 2003[76]	Sample size: 110 Age (mean/range): 68/NR Race: NR % male: 55 # sites: 12 Location: Australia, Italy, Netherlands, UK, Canada, and Belgium	Design: RCT Duration: 8 weeks	Inclusion: Upper gastrointestinal malignancies/Weight-losing cancer patients/Histologically proven GI neoplasm Exclusion: Karnofsky score < 60/Chemotherapeutic treatment/Radiation therapy/Elective surgery/Renal disease/Diabetes mellitus/HIV/AIDS/Systemic medication or supplement use	Surgery	1	Isoenergetic control diet 474.0 ml/day
					2	N3 fatty acids 474.0 ml/day plus Vitamin E, Vitamin C, Selenium
Gianotti, 1999[77]	Sample size: 50 Age (mean/range): 62/NR Race: NR % male: 60 # sites: 1 Location: Italy	Design: RCT Duration: 14 days	Inclusion: Upper gastrointestinal malignancies/Undergoing abdominal surgery/Colorectal cancer Exclusion: Immunosuppressive medications use/Evidence of infection/Chemotherapeutic treatment/Previous abdominal or pelvic radiotherapy/Renal disease/Impaired liver function/Cardiac dysfunction/Need for emergency	Surgery	1	Enteral standard diet 1.0 Liter/DY X 14.0 DY plus N6 polyunsaturated fat
					2	'N3 fatty acids 1.0 Liter/DY X 14.0 DY plus N6 polyunsaturated fat
Gianotti, 1997[71]	Sample size: 260 Age (mean/range): 64/NR Race: NR % male: 56 # sites: 1 Location: Italy	Design: RCT Duration: 7 days	Inclusion: Upper gastrointestinal malignancies/Undergoing abdominal surgery Exclusion: Renal disease/Impaired liver function/Pulmonary dysfunction/Cardiac dysfunction/Evidence of infection/Immune disorders	Surgery	1	Enteral standard diet variable dose
					2	Standard TPN variable dose
					3	N3 fatty acids variable dose

* NR = Not Reported.

Appendix C. Evidence Tables (continued)

Table C.2.1. Evidence table of clinical trials of the clinical effects of omega-3 fatty acids on clinical outcomes after cancer treatment.*

Heller, 2004[75]	Sample size: 44 Age (mean/range): 61/NR Race: NR % male: 73 # sites: 1 Location: Germany	Design: RCT Duration: 5 days	Inclusion: Carcinoma of the gastrointestinal tract or pancreas /Undergoing abdominal surgery Exclusion: Age <18 or >80 years, ASA status >3, BMI <16 or >30, hypertiglyceridemia, pregnancy, hyperthyroidism, chronic liver disease, pancreatitis, HIV infection, hepatitis, severe cardiac or renal disease or medication with insulin, corticosteroids, cytostatics or cycoloxygenase inhibitors.	Surgery	1	TPN
					2	TPN containing omega-3 fatty acids
Kenler, 1996[61]	Sample size: 35 Age (mean/range): 64/18-80 Race: NR % male: 74 # sites: 1 Location: US	Design: RCT Duration: 7 days	Inclusion: Upper gastrointestinal malignancies/Undergoing abdominal surgery Exclusion: Evidence of infection/Steroids use/Renal disease/Cardiac dysfunction/HIV/AIDS	Surgery	1	Soybean oil, Osmolite dosage NR plus Vitamin E, Vitamin C
					2	Fish oil, Soybean oil, Canola oil dosage variable plus Vitamin E, Vitamin C

* NR = Not Reported.

Appendix C. Evidence Tables (continued)

Table C.2.1. Evidence table of clinical trials of the clinical effects of omega-3 fatty acids on clinical outcomes after cancer treatment.*

First Author, Year	Study Characteristics	Study Design Duration	Eligibility criteria	Cancer treatment	Arm	Interventions Dosage/Duration
McCarter, 1998[62]	Sample size: 38 Age (mean/range): 64/NR Race: NR % male: 55 # sites: 1 Location: US	Design: RCT Duration: 30 days	Inclusion: Upper gastrointestinal malignancies/Undergoing abdominal surgery/Age=18 Exclusion: Evidence of infection/Immunosuppressive medications use/Impaired liver function/Serum creatinine > 2 mg/dl/Radiation therapy/HIV/AIDS/Diabetes mellitus/Pregnancy	Surgery	1	Standard nutritional supplement, Soybean oil dosage NR plus Vitamin C, Retinol, Carotene, Vitamin E
					2	Standard nutritional supplement, Arginine, Soybean oil dosage NR plus Vitamin C, Retinol, Carotene, Vitamin E
					3	Fish, Standard nutritional supplement, Arginine, Soybean oil dosage NR plus Vitamin C, Retinol, Carotene, Vitamin E
Preshaw, 1979[79]	Sample size: 47 Age (mean/range): 68/NR Race: NR % male: NR # sites: 1 Location: Canada	Design: CCT Duration: 6 days	Inclusion: Upper gastrointestinal malignancies/Undergoing abdominal surgery/Age=75 Exclusion: Cardiac dysfunction	Surgery	1	IV fluids, Amino acids dosage variable
					2	IV fluids, Soybean oil, Amino acids dosage variable

* NR = Not Reported.

Appendix C. Evidence Tables (continued)

Table C.2.1. Evidence table of clinical trials of the clinical effects of omega-3 fatty acids on clinical outcomes after cancer treatment.*

First Author, Year	Study Characteristics	Study Design Duration	Eligibility criteria	Cancer treatment	Arm	Interventions Dosage/Duration
Schilling, 1996[72]	Sample size: 41 Age (mean/range): 59/NR Race: NR % male: 54 # sites: 1 Location: Switzerland	Design: RCT Duration: 10 days	Inclusion: Upper gastrointestinal malignancies/Undergoing abdominal surgery Exclusion: Renal disease/Food allergy history/Pregnancy/Evidence of infection/Steroids use/Immunosuppressive medications use/Radiation therapy/Diabetes mellitus	Surgery	1	Enteral standard diet dosage NR
					2	IV fluids dosage NR
					3	N3 fatty acids, Arganine, omega-6 fatty acids dosage NR plus Selenium
Senkal, 1997[74]	Sample size: 154 Age (mean/range): 66/18-80 Race: NR % male: NR # sites: 3 Location: Germany	Design: RCT Duration: 31 days	Inclusion: Upper gastrointestinal malignancies/Undergoing abdominal surgery/Minimum uptake of 3000 of study diet preoperatively Exclusion: Immunosuppressive medications use/Radiation therapy/Chemotherapeutic treatment/Immune disorders/Diabetes mellitus/Pregnancy	Surgery	1	Isoenergetic control diet, omega-6 fatty acids variable dosage plus n-6 polyunsaturated fat, Vitamin C, Retinol, Tocopherols, Selenium, Molybdenum
					2	N3 fatty acids, Arginine, omega-6 fatty acids variable dosage plus n-6 polyunsaturated fat, Vitamin C, Retinol, Tocopherols, Selenium, Molybdenum

* NR = Not Reported.

Appendix C. Evidence Tables (continued)

Table C.2.1. Evidence table of clinical trials of the clinical effects of omega-3 fatty acids on clinical outcomes after cancer treatment.*

First Author, Year	Study Characteristics	Study Design Duration	Eligibility criteria	Cancer treatment	Arm	Interventions Dosage/Duration
Senkal, 1999[73]	Sample size: 154 Age (mean/range): 66/18-80 Race: NR % male: 56 # sites: NR Location: Germany	Design: RCT Duration: 10 days	Inclusion: Upper GI surgery/Histologically proven GI neoplasm/Minimum uptake of 3000 of study diet preoperatively Exclusion: Immunosuppressive medications use/Chemotherapeutic treatment/Cardiac dysfunction/Radiation therapy/Renal disease/Impaired liver function/Chronic disease history/Endocrine disease	Surgery	1	Isoenergetic control diet, Standard hospital diet dosage NR plus Linoleic Acid, N6 polyunsaturated fat, Vitamin E, Carotene, Vitamin C, Retinol
					2	N3 fatty acids, Standard hospital diet 1.0 G/DY X 10.0 DY plus Linoleic Acid, N6 polyunsaturated fat, Vitamin E, Carotene, Vitamin C, Retinol
Swails, 1997[63]	Sample size: 18 Age (mean/range): 68/18-80 Race: NR % male: 61 # sites: 1 Location: US	Design: RCT Duration: 7 days	Inclusion: Upper gastrointestinal malignancies/Undergoing abdominal surgery Exclusion: Renal disease/Cardiac dysfunction/Evidence of infection/HIV/AIDS/Steroids us	Surgery	1	Corn oil, Soybean oil variable dosage plus Linoleic Acid, Vitamin E, Vitamin C
					2	Fish oil, Canola oil, Soybean oil variable dosage plus Selenium, Manganese, Linoleic Acid

* NR = Not Reported.

Appendix C. Evidence Tables (continued)

Table C.2.1. Evidence table of clinical trials of the clinical effects of omega-3 fatty acids on clinical outcomes after cancer treatment.*

First Author, Year	Study Characteristics	Study Design Duration	Eligibility criteria	Cancer treatment	Arm	Interventions Dosage/Duration
Vignali, 1995[78]	Sample size: 43 Age (mean/range): 60.3/NR Race: Caucasian % male: 63 # sites: 1 Location: Italy	Design: RCT Duration: 8 days	Inclusion: Gastric cancer, Pancreatic cancer, Surgery for tumor Exclusion: NR	Surgery	1	Enteral standard diet, Arginine, RNA, omega-3 fatty acids
					2	Enteral standard diet
					3	Olive oil

* NR = Not Reported.

Appendix C. Evidence Tables (continued)

Table C.2.2. Evidence table of clinical trials of the clinical effects of omega-3 fatty acids on clinical outcomes after cancer treatment.

First Author, Year	Outcomes Results	Applicability Funding source Quality
Braga, 2002[64]	Postoperative complications: RR: 0.35 (95% CI 0.19, 0.67) Length of stay: Mean difference: -2.5 days (95% CI –3.5, -3.5) Mortality: Placebo: 1/10 O-3: 1/100 Nutrition: NR Mean weight loss: NR	Applicability: IIB Funding source: NR Jadad: 3 Concealment of allocation: NR
Braga, 2002[65]	Postoperative complications: RR: 0.54 (95% CI 0.27, 1.13) Length of stay: Mean difference: -2.7 days (95% CI –4.0, -1.4) Mortality: Placebo: 1/10 O-3: 2/50 Nutrition: NR Mean weight loss: NR	Applicability: IIB Funding source: NR Jadad: 3 Concealment of allocation: NR

*NR = not reported, O-3 = omega-3, g = gram, kcal = kilocalories, mg = milligrams, dl = deciliter, kg = kilograms; † mean values.

Appendix C. Evidence Tables (continued)

Table C.2.2. Evidence table of clinical trials of the clinical effects of omega-3 fatty acids on clinical outcomes after cancer treatment.

First Author, Year	Outcomes Results	Applicability Funding source Quality
Braga, 1995[66]	Postoperative complications: RR: 0.46 (95% CI 0.09, 2.30) Length of stay: Mean difference: -1.7 days (95% CI –4.5, -1.0) Mortality: NR Nutrition: NR Mean weight loss: NR	Applicability: IIB Funding source: NR Jadad: 2 Concealment of allocation: NR
Braga, 1999[67]	Postoperative complications: RR: 0.43 (95% CI 0.21, 0.89) Length of stay: NR Mortality: NR Nutrition: Caloric intake kcal/day; Nitrogen intake g/day; Albumin mg/dl; Transferrin mg/dl; Prealbumin mg/dl Placebo: NR; NR; 3.7; 218; 18 O-3: NR; NR; 3.7; 223; 23 Reported Testing: NR; NR; NR; NR; p<0.05 Mean weight loss: NR	Applicability: IIB Funding source: NR Jadad: 4 Concealment of allocation: NR

*NR = not reported, O-3 = omega-3, g = gram, kcal = kilocalories, mg = milligrams, dl = deciliter, kg = kilograms; † mean values.

Appendix C. Evidence Tables (continued)

Table C.2.2. Evidence table of clinical trials of the clinical effects of omega-3 fatty acids on clinical outcomes after cancer treatment.

First Author, Year	Outcomes Results	Applicability Funding source Quality
Daly, 1992[68]	Postoperative complications: RR: 0.38 (95% CI 0.13, 1.07) Length of stay: Mean difference: -6.0 days (95% CI -7.09, -4.91) Mortality: Placebo: 0/41 O-3: 1/36 Nutrition: Caloric intake kcal/day: Placebo 1285; O-3 1421; Reported Testing NR Nitrogen intake g/day: Placebo 9; O-3 15.6; Reported Testing p=0.001 Albumin mg/dl: Placebo 2.0; O-3 2.1; Reported Testing NR Transferrin mg/dl: Placebo 152; O-3 161; Reported Testing NR Prealbumin mg/dl: Placebo NR; O-3 NR; Reported Testing NR Mean weight loss: NR	Applicability: IIB Funding source: Government, private, industry Jadad: 1 Concealment of allocation: Y

*NR = not reported, O-3 = omega-3, g = gram, kcal = kilocalories, mg = milligrams, dl = deciliter, kg = kilograms; † mean values.

Appendix C. Evidence Tables (continued)

Table C.2.2. Evidence table of clinical trials of the clinical effects of omega-3 fatty acids on clinical outcomes after cancer treatment.

First Author, Year	Outcomes Results	Applicability Funding source Quality
Daly, 1995[69]	Postoperative complications: RR: 0.23 (95% CI 0.07, 0.73) Length of stay: Mean difference: -4.4 days (95% CI -7.85, -0.95) Mortality: NR Nutrition: Caloric intake kcal/day; Nitrogen intake g/day; Albumin mg/dl; Transferrin mg/dl; Prealbumin mg/dl Placebo: 1232; 10.1; 3.1; 181; 17 O-3: 1067; 11.9; 3.1; 190; 16 Reported Testing: NR; NR; NR; NR; NR Mean weight loss: NR	Applicability: IIB Funding source: NR Jadad: 1 Concealment of allocation: Y

*NR = not reported, O-3 = omega-3, g = gram, kcal = kilocalories, mg = milligrams, dl = deciliter, kg = kilograms; † mean values.

Appendix C. Evidence Tables (continued)

Table C.2.2. Evidence table of clinical trials of the clinical effects of omega-3 fatty acids on clinical outcomes after cancer treatment.

First Author, Year	Outcomes Results	Applicability Funding source Quality
Di Carlo, 1999[70]	Postoperative complications: RR: 0.53 (95% CI 0.14, 1.95) Length of stay: Mean difference: -1.5 days (95% CI –4.6, -1.6) Mortality: Placebo: 1/33 O-3: 0/35 Nutrition: Caloric intake kcal/day: Placebo 1550, O-3 1580, Reported Testing NR Nitrogen intake g/day: Placebo NR, O-3 NR, Reported Testing NR Albumin mg/dl: Placebo NR, O-3 NR, Reported Testing NR Transferrin mg/dl: Placebo NR, O-3 NR, Reported Testing NR Prealbumin mg/dl: Placebo NR, O-3 NR, Reported Testing NR Mean weight loss: NR	Applicability: IIB Funding source: NR Jadad: 1 Concealment of allocation: NR
Fearon, 2003[76]	Postoperative complications: NR Length of stay: NR Mortality: Placebo: 11/105 O-3: 16/95 Nutrition: NR Mean weight loss: Placebo: 0.37 kg/month O-3: 0.25 kg/month	Applicability: IIB Funding source: Industry Jadad: 5 Concealment of allocation: Y

*NR = not reported, O-3 = omega-3, g = gram, kcal = kilocalories, mg = milligrams, dl = deciliter, kg = kilograms; † mean values.

Appendix C. Evidence Tables (continued)

Table C.2.2. Evidence table of clinical trials of the clinical effects of omega-3 fatty acids on clinical outcomes after cancer treatment.

First Author, Year	Outcomes Results	Applicability Funding source Quality
Gianotti, 1999[77]	Postoperative complications: NR Length of stay: NR Mortality: NR Nutrition: Caloric intake kcal/day; Nitrogen intake g/day; Albumin mg/dl; Transferrin mg/dl; Prealbumin mg/dl Placebo: NR; NR; 3.7; NR; 18 O-3: NR; NR; 3.7; NR; 26 Reported Testing: NR; NR; NR; NR; <0.05 Mean weight loss: NR	Applicability: IIB Funding source: NR Jadad: 4 Concealment of allocation: NR

*NR = not reported, O-3 = omega-3, g = gram, kcal = kilocalories, mg = milligrams, dl = deciliter, kg = kilograms; † mean values.

Appendix C. Evidence Tables (continued)

Table C.2.2. Evidence table of clinical trials of the clinical effects of omega-3 fatty acids on clinical outcomes after cancer treatment.

First Author, Year	Outcomes Results	Applicability Funding source Quality
Gianotti, 1997[71]	Postoperative complications: RR: 0.2365(95% CI 0.35, 1.22) Length of stay: Mean difference: -3.5 days (95% CI –5.2, -1.0) Mortality: Placebo: 2/77 O-3: 3/77 Nutrition: Caloric intake kcal/day; Nitrogen intake g/day; Albumin mg/dl; Transferrin mg/dl; Prealbumin mg/dl Placebo: NR; NR; NR; NR; 18 O-3: NR; NR; NR; NR; 23 Reported Testing: NR; NR; NR; NR; p<0.01 Mean weight loss: NR	Applicability: IIB Funding source: NR Jadad: 2 Concealment of allocation: NR
Heller, 2004[75]	Postoperative complications: NR Length of stay: Mean difference: 0 days (95% CI –25, 25) Mortality: NR Nutrition: NR Mean weight loss: Placebo: 1.1 ± 2.2 kg over length of hospital stay O-3: 0.0 ± 2.9 kg over length of hospital stay No significant difference between groups	Applicability: IIB Funding source: Industry Jadad: 5 Concealment of allocation: Yes

*NR = not reported, O-3 = omega-3, g = gram, kcal = kilocalories, mg = milligrams, dl = deciliter, kg = kilograms; † mean values.

Appendix C. Evidence Tables (continued)

Table C.2.2. Evidence table of clinical trials of the clinical effects of omega-3 fatty acids on clinical outcomes after cancer treatment.

First Author, Year	Outcomes Results	Applicability Funding source Quality
Kenler, 1996[61]	Postoperative complications: RR: 0.91 (95% CI 0.38, 2.16) Length of stay: Mean difference: 0.7 days (95% CI -2.80, 4.20) Mortality: Placebo: 1/18 O-3: 1/17 Nutrition: Caloric intake kcal/day: Placebo 1050; O-3 1102; Reported Testing p = 0.63 Nitrogen intake g/day: Placebo NR; O-3 NR; Reported Testing NR Albumin mg/dl: Placebo NR; O-3 NR; Reported Testing NR Transferrin mg/dl: Placebo NR; O-3 NR; Reported Testing NR Prealbumin mg/dl: Placebo NR; O-3 NR; Reported Testing NR Mean weight loss: NR	Applicability: IIB Funding source: Industry Jadad: 1 Concealment of allocation: NR

*NR = not reported, O-3 = omega-3, g = gram, kcal = kilocalories, mg = milligrams, dl = deciliter, kg = kilograms; † mean values.

Table C.2.2. Evidence table of clinical trials of the clinical effects of omega-3 fatty acids on clinical outcomes after cancer treatment.

First Author, Year	Outcomes Results	Applicability Funding source Quality
McCarter, 1998[62]	Postoperative complications: NR Length of stay: Mean difference: 2.0 days (95% CI –7.45, 11.45) Mortality:NR Nutrition: NR Mean weight loss: NR	Applicability: IIB Funding source: Industry Jadad: 4 Concealment of allocation: NR
Preshaw, 1979[79]	Postoperative complications: NR Length of stay: NR Mortality: NR Nutrition: NR Mean weight loss: Placebo: 2.5 kg over 2 weeks O-3: 3.9 kg over 2 weeks	Applicability: NR Funding source: RN Jadad: 0 Concealment of allocation: NR

*NR = not reported, O-3 = omega-3, g = gram, kcal = kilocalories, mg = milligrams, dl = deciliter, kg = kilograms; † mean values.

Appendix C. Evidence Tables (continued)

Table C.2.2. Evidence table of clinical trials of the clinical effects of omega-3 fatty acids on clinical outcomes after cancer treatment.

First Author, Year	Outcomes Results	Applicability Funding source Quality
Schilling, 1996[72]	Postoperative complications: RR: 0.50 (95% CI 0.15, 1.61) Length of stay: Mean difference: 0.5 days (95% CI –7.5, 8.5) Mortality: NR Nutrition: Placebo: Caloric intake 30.4 kcal/kg/day; Nitrogen intake NR g/day; Albumin NR mg/dl; Transferrin NR mg/dl; Prealbumin NR mg/dl O-3: Caloric intake 17.4 kcal/kg/day; Nitrogen intake NR g/day; Albumin NR mg/dl; Transferrin NR mg/dl; Prealbumin NR mg/dl Reported Testing: NR Mean weight loss: NR	Applicability: IIB Funding source: Industry Jadad: 2 Concealment of allocation: NR
Senkal, 1997[74]	Postoperative complications: RR: 0.71 (95% CI 0.41, 1.21) Length of stay: Mean difference: -3.6 days (95% CI –4.5, -2.7) Mortality: NR Nutrition: NR Mean weight loss: NR	Applicability: IIB Funding source: NR Jadad: 3 Concealment of allocation: NR

*NR = not reported, O-3 = omega-3, g = gram, kcal = kilocalories, mg = milligrams, dl = deciliter, kg = kilograms; † mean values.

Appendix C. Evidence Tables (continued)

Table C.2.2. Evidence table of clinical trials of the clinical effects of omega-3 fatty acids on clinical outcomes after cancer treatment.

First Author, Year	Outcomes Results	Applicability Funding source Quality
Senkal, 1999[73]	Postoperative complications: RR: 0.54 (95% CI 0.27, 1.10) Length of stay: Mean difference: -3.6 days (95% CI –4.9, -2.4) Mortality: NR Nutrition: NR Mean weight loss: NR	Applicability: IIB Funding source: NR Jadad:3 Concealment of allocation: NR
Swails, 1997[63]	Postoperative complications: RR: 1.67 (95% CI 0.52, 5.39) Length of stay: NR Mortality: Placebo: 0/10 O-3: 0/8 Nutrition: Caloric intake kcal/day: Placebo 1047; O-3 1010; Reported Testing NR Nitrogen intake g/day: Placebo NR; O-3 NR; Reported Testing NR Albumin mg/dl: Placebo NR; O-3 NR; Reported Testing NR Transferrin mg/dl: Placebo NR; O-3 NR; Reported Testing NR Prealbumin mg/dl: Placebo NR; O-3 NR; Reported Testing NR Weight: NR	Applicability: IIB Funding source: Jadad: 2 Concealment of allocation: NR

*NR = not reported, O-3 = omega-3, g = gram, kcal = kilocalories, mg = milligrams, dl = deciliter, kg = kilograms; † mean values.

Table C.2.2. Evidence table of clinical trials of the clinical effects of omega-3 fatty acids on clinical outcomes after cancer treatment.

First Author, Year	Outcomes Results	Applicability Funding source Quality
Vignali, 1995[78]	Postoperative complications: NR Length of stay: NR Mortality: NR Nutrition: Caloric intake kcal/day; Nitrogen intake g/day; Albumin mg/dl; Transferrin mg/dl; Prealbumin mg/dl Placebo: NR; NR; 3.2; NR; 17 O-3: NR; NR; 3.4; NR; 20 Reported Testing: NR; NR; NR; NR; NR Weight: NR	Applicability: IIIB Funding source: NR Jadad: 2 Concealment of allocation: NR

*NR = not reported, O-3 = omega-3, g = gram, kcal = kilocalories, mg = milligrams, dl = deciliter, kg = kilograms; † mean values.

Appendix C. Evidence Tables (continued)

Table C.3.1. Systematic Reviews of Tumor Development.

Author, Year	Model(s)	Outcomes Assessed	Conclusions	Years included	Completeness of Search	Databases	Inclusion Criteria	Conclusions Follow from Data?
Mammary								
Fay, 1997[80] Meta-analysis	Rats and mice	Effects of n-6 PUFA, n-3 PUFA, monounsaturated fatty acids, saturated fatty acids, and energy restriction on incidence of mammary tumors in rats and mice.*	Substitution of n-3s for nonfat calories appeared to have a small, non-significant (p=0.62) protective effect on incidence of tumor development. No conclusions about other aspects of tumor growth such as time to onset, size, number of tumors.†	1966-1994	Systematic	Medline used to update a database created in 1990 by author	Random assignment to treatment groups; study of sufficient duration to allow reporting of final tumor incidence; animals all of same species/strain; at least two treatment groups per study; all groups followed for same duration; semipurified diets; only dietary interventions; fat sources reported; animals in one study all receive same carcinogenic insult at same age; carcinogen is not from transplanted tumors and not dietary	Yes

* Several means used to introduce n-3 PUFA: substituting for nonfat calories, substituting for n-6 calories, use of menhaden oil, which is high in saturated and monounsaturated fat also. Sensitivity analysis done by separating data on S-D rats from rest of rats, separating rats and mice. † Effect may be supported by studies involving transplanted tumors, but these studies not included in analysis.

Appendix C. Evidence Tables (continued)

Table C.3.1. Systematic Reviews of Tumor Development.

Author, Year	Model(s)	Outcomes Assessed	Conclusions	Years included	Completeness of Search	Databases	Inclusion Criteria	Conclusions Follow from Data?
Prostate								
Kolonel, 1999[81]	Multiple models of mouse tumor induction with chemicals, irradiation, and prolonged testosterone‡	Effects of dietary fat on promotion, inhibition of tumor growth	Mixed effects observed for total dietary fat. Fish oils containing high levels of EPA and DHA generally suppress prostate tumor growth in vivo and in vitro; however, one study found that EPA was inhibitory only at high concentrations. Thus fish oil may not decrease risk and nothing is known about the possible mechanism(s) by which it alters tumor development.(based on 4 studies)	1940-1998; 1986-1996 for n-3 studies	Systematic	Medline	English language articles only	Yes, although no real conclusions, only suggested research directions.

‡ Animal models of prostate cancer are nearly non-existent. No record exists of spontaneous neoplasms in mice and very low incidence of cancerous lesions in rats (only 2 reports in rats since 1963). Also, rodent prostate differs anatomically from human. Transgenic mouse models for prostatic neoplasia offer some hope of being able to research effects of various environmental factors.

Appendix C. Evidence Tables (continued)

Table C.3.1. Systematic Reviews of Tumor Development.

Author, Year	Model(s)	Outcomes Assessed	Conclusions	Years included	Completeness of Search	Databases	Inclusion Criteria	Conclusions Follow from Data?
Colon								
Zhao, 1991[83]	Sprague Dawley (SD) and Fischer 344 rats, carcinogen-induction	Effect of fat intake on incidence of colon carcinoma and number of tumors, controlling for calories	14 studies of rats identified. N-3s represented 0-6.9 percent of total body weight. N-3 fatty acids appeared to be negatively associated with colon carcinoma incidence for both types of rats combined. Non-n 3s (n 6s) appeared to promote tumors in Fischer 344s but not in SD rats.	1969-1990	Systematic	Medline	Inclusion of information on dietary composition, including fat content; inclusion of incidence data; random assignment to treatment groups feeding in usual manner (probably to exclude feeding by gavage, e.g.)	Yes, but not sure of validity or effect of method used to calculate fat intake (much info lacking from reports)
Corpet, 2003[92]	Min mouse, a mutant that spontaneously develops multiple intestinal neoplasias secondary to a mutation in the Apc gene, similar to humans with familial adenomatous polyposis	Effect of a variety of putative dietary cancer preventive agents on tumor yield in the colon and small intestine.	All studies involving fish oil and min mouse come from one published report (Paulsen et al., 1997): 0.4, 1.25, and 2.5% of diet in males and females, 17 weeks duration from 1 wk of age. Effects were consistent across the animal models. Decreased tumor yield in small intestine by 60-70 percent. Not dose dependent. Effect in colon not significant.	1990 (1997)-2002	Systematic	ISI Current Contents, Medline, AACR Website 1990-2002	Plausibility, inclusion of quantitative data	Yes, although limited

Appendix C. Evidence Tables (continued)

Table C.3.1. Systematic Reviews of Tumor Development.

Author, Year	Model(s)	Outcomes Assessed	Conclusions	Years included	Completeness of Search	Databases	Inclusion Criteria	Conclusions Follow from Data?
Corpet, 2002[84]	Carcinogen-induced colon tumors in Fischer and Sprague-Dawley rats	Effect of a wide variety of agents on inhibition of Aberrant crypt foci (ACF); tumor number	AGF Inhibition: Perilla oil: 74-91% DHA: 64-65% Fish oil: 50% Tumor Reduction: Fish oil: 31-64% (somewhat dose-dependent) Perilla oil: 52% Effects seen only in Fischer rats. N-3s not ranked among most potent agents overall.	1989-2001	Systematic but omitted studies with no or insignificant effect	Medline, CCLS, AACR website, Carcinogenesis and Cancer Letters journals	Plausibility, inclusion of quantitative data, no use toxic agents, only those reporting a significant protective effect (as the point of the review was to identify agents for clinical trial testing). Only most potent agent and dose included from each study	Yes

Table C.3.2. Non-systematic reviews of n-3 Fatty Acids and Tumor Growth and Development.

Author, Year	Model(s)	Outcomes	Conclusions	Years
Mammary/Breast tumors				
Cave, 1991[82]	Carcinogen induction models: NMU-induced mammary tumors in Buffalo rats and transplanted mammary tumors DMBA mammary tumor model	Effects on Tumor incidence and latency of diets high in fish oil (FO) vs. corn oil	Increasing % dietary n-3s (FO 0.5-20%) progressively lengthened tumor latency period (in some studies) and decreased incidence and burden	75-89
	Transplant models: R3230AC mammary AC to female Fischer 344 rats; BALB-c mammary AC to Balb/c mice	Same	F 344 model: reduced transplant growth Balb/C model: tumor growth inhibition; suppression of effect of corn oil; increased rate of tumor cell loss (apoptosis?)	
	BN 472 mammary AC transplanted into BN/Bi mice; crossover	Crossover 25% FO and 25% cocoa butter diets	Tumor inhibitory effect of FO greater when diet begun before transplantation	
	Human mammary CA MX-1 transplanted into heterozygous BALB/c nu/+ athymic nude mice	10% FO vs. 10% corn oil diet	Growth rates of tumor cells depressed by fish oil; Transplants in FO-fed rats more responsive to chemotherapeutic drugs than those in CO-fed rats	
Fernandes, 1991[102]	Nude mice transplanted with MCF-7 (E_2-receptor-positive) human breast cancer cells; MDA-MB231 (E_2-receptor-negative)	Modulation of mammary tumor development by n-3s	Rate of tumor cell growth and volume significantly lower in fish-oil fed mice cf. corn-oil fed: No data	75-90
Noguchi, 1995[103]	Rat in vivo; mouse transplants; human cell culture;	Breast Carcinoma tumorigenesis, Proliferation: effects of n 6s and n 3s (DHA and EPA)	DHA and EPA suppress breast carcinoma tumorigenesis and cell proliferation. No data.	75-94
Gonzalez, 1995[104]	Multiple animal and in vitro models discussed	Tumor suppression by n-3s	Possibility that lipid peroxidation secondary to high fish oil ingestion may be responsible for inhibition or suppression of mammary tumor growth, poss. through formation of cytotoxic compounds	56-92

Table C.3.2. Non-systematic reviews of n-3 Fatty Acids and Tumor Growth and Development.

Author, Year	Model(s)	Outcomes	Conclusions	Years
Klurfeld, 1995[94]	DMBA-induced rat mammary tumor model	Energy restriction vs. fat restriction	Ad lib, low fat diets produce more tumors than energy restricted higher fat diets, regardless of source of fat; also, use of n-3s as sole fat source may inhibit tumor growth because mammary tumors require some n-6 FA; small amount of n-6+FO leads to increased growth in mammary tumors but suppression in others	'47-'89
Cave, 1997[91]	rodent mammary tumor models: transplanted tumors to nude, athymic mice, carcinogen-induced tumors, DES-induced tumors, and x-ray induced tumors	Tumor promotion by n-3s	Increasing % dietary n-3s (menhaden oil 0.5-20%) progressively lengthened tumor latency period and decreased incidence and burden; fish oil, purified EPA and DHA, high levels ALN also reduced growth in tumor transplant models; fish oil also enhanced effects of several types of chemotherapy in athymic mouse model	42-95
Stoll, 1998[105]	Human mammary cell culture; explants; chemically-induced carcinogenesis in rat	Inhibition of growth, metastasis; Protex against induced carcinogenesis by n-3 FAs and antioxidants	N-3s, increased ratio n-3s/n-6s inhibit growth, metastasis; protect against induced CA: No data. Role of antioxidants alone vs. with n-3s unclear	75-97
Stoll, 1998[106]	Human mammary cell culture; explants; chemically-induced mammary tumors	Protection against growth by n-3s	n-3s inhibit growth; incidental to main point of review: insulin resistance and BC risk (insulin resistance may be one means by which n-3s influence tumorigenesis)	87-97
Rose, 2000[97]	MDA-MB-231 breast cancer cells in nude mice (part of a review on dietary FA and angiogenesis)	Effect of DHA on tumor mass	DHA inhibited tumor mass increase by a combination of decreased cell proliferation, increased apoptosis, and reduced angiogenesis	95-99
Sinclair, 2002[107]	Rat mammary tumor (mostly human models cited)	Tumor growth effects of *α-linolenic acid*	α-linolenic acid plus high vitamin E promoted tumor growth cf. α-linolenic acid without E (most of paper reviews mechanisms of α-linolenic acid's effects). Suggests peroxidative damage (toxic products) inhibits tumor growth, which may depend on dietary oxidative status. Role may not be solely as precursor to EPA, DHA. Conversion to EPA, DHA actually inefficient	30-02

Table C.3.2. Non-systematic reviews of n-3 Fatty Acids and Tumor Growth and Development.

Author, Year	Model(s)	Outcomes	Conclusions	Years
Prostate tumors				
Cave, 1991[82]	Athymic nude mice (nu/nu) implanted with DU-145 cultured human prostate cancer cells	Effect of corn oil vs. FO on tumor volume and weight	Few animal models. Nu/nu mice on high FO diets had signif lower tumor volumes and weights, altered chemistry	
	Nude mice (Balb/c CD-1) transplanted with DU-145 cells at one of two doses	Diet initiated 3 weeks prior to transplant	FO diet retarded progression of transplanted cells but only at lower dose of cells (initial tumor burden)	
Colon tumors				
Cave, 1991[82]	Male Fischer344 rats induced with AOM (Reddy)	4%, 22.5% MO+1%CO vs. 5%, 23.5% CO, 34 wks. Adenocarcinoma incidence and number of tumors in large intestine (may want to mention timing of carcinogen vs diet?)	MO and low CO diets resulted in significantly lower tumor number in large intestine cf. high CO. Possible mechanisms: 1) n-3s may inhibit 2° bile acids or 2) n-3s may alter colon eicosanoid metabolism.	77-89
	Same model with 6 combinations of oils (Reddy)	4% MO+1%CO; 5.9%MO+17.6%CO 11.8%MO+11.8%CO 17.6%MO+5.9%CO; 5%CO; 23.5%CO 38wks	No increase in tumor incidence or number in 1st, 2nd, 3rd, 4th, 5th groups; 6th group had significant increase in incidence. Total number of tumors was lower in animals in groups 1,4,5. Therefore, high fat intake is necessary but not sufficient: N-3/n-6 ratio important.	
	Similar model with Donryu rats (Minoura)	n-3 (EPA) vs. n-6 (LA) diet	Lower tumor incidence assoc. w/n-3 diet also assoc. w/lower tumor levels of PGE_2. May have direct or indirect effx.	
	SD rats induced with DMH	17%MO vs. 17%CO	Signif lower colorectal tumor number in MO-fed rats but no difference in plasma peroxide concentrations, which may or may not reflect colon peroxide levels.	
	Balb/c ByJ mice injected with CT-26 colon carcinoma cells	5% Safflower Oil(SO) 24.7%SO 5%MO 24.7%MO Effect on tumor size, number, mortality rate	Tumor size largest in 24.7%SO followed by 5%SO. 5% and 24.7% MO lowest and not different (i.e. No dose dependence for MO). 24.7%SO had increased mortality rate and tumor number cf. other groups. Proposed that n-3s compete with and inhibit the effx of n-6s on some process required for growth and survival.	

Table C.3.2. Non-systematic reviews of n-3 Fatty Acids and Tumor Growth and Development.

Author, Year	Model(s)	Outcomes	Conclusions	Years
Klurfeld, 1995[94]	DMH-induced rat colon tumor model	Energy restriction vs. fat restriction	Ad lib, low fat diets produce more tumors than energy restricted higher fat diets, regardless of source of fat DMBA and DMH tumors even more sensitive to effects of energy restriction than DMBA tumors. Ad lib fed rats may actually be obese; small amount of n-6+FO leads to decreased growth on colon tumors	'47-'89
Reddy, 1992[85]	Same as first two Reddy studies above and Minoura	Same as reviewed by Cave plus a third study with crossover design (low corn oil, high corn oil, high fish oil for 9 weeks; during last two weeks, two weekly injections of AOM; three days after 2nd injection, animals switched to difft. diet or kept on same diet for 42 weeks) to test effect of diets on AOM-induced tumor initiation	High fish oil diet decreased colon tumor incidence and number when fed during initiation or post-initiation. Possible mechanisms may involve decrease in secondary bile acids (which fn as tumor promoters in gut and induce ornithine decarboxylase) and modification of gut flora, which modifies formation of tumor promoting substances in gut. Alternatively, could be due to n-3-mediated alterations in (inhibition of) PG synthesis; finally, n-3s may increase the rate of detoxification of AOM	78-91

Appendix C. Evidence Tables (continued)

Table C.3.2. Non-systematic reviews of n-3 Fatty Acids and Tumor Growth and Development.

Author, Year	Model(s)	Outcomes	Conclusions	Years
Ma, 1996[93]	Same models as Cave review plus those post '90, but poor description of models AOM-treated mice (Deschner)			83-93
		Various ratios of n-3/n-6 effx on adenomatous proliferative pattern, tumor incidence in colon	n-3/n-6 ratio of 1 prevented prolif. and tumor incidence	
	DMH-induced rats (Takahashi, 93)			
	DMH-induced SD rats (Kuratko and Pence, 92)	IG gavage of DHA effx on formation and growth of aberrant crypt foci	Suppressed formation and growth of aberrant foci	
		19% MO vs 19% beef tallow vs. 20% CO effects on colon tumor metabolism	MO increased lipid peroxidation in DMH-induced tumors	
			Conclusion: n-3s may inhibit tumor formation	
Pancreatic tumors				
Cave, 1991[82]	AZA-treated Wistar rats to induce preneoplastic atypical acinar cell nodules (AACN) and adenocarcinomas (O'Connor)	1) 20% MO vs. 20% CO	MO reduced number and size of preneoplastic lesions	
		2) 9 dietary groups with n-3/n-6 ratios varying from 0.01 to 7.	As n-3/n-6 increased, preneoplastic development decreased significantly, along with levels of PGE_2.	
		3) Crossover study post tumor inductions. 2 months each 20% MO and 20% CO and the reverse (2 control groups were not switched).	Highest to lowest number of tumors: All CO diet, switching from MO to CO, switching from CO to MO and all MO. Concluded n-3/n-6 ratio significantly influences AACN development.	
Other				
Avula, 2000[87]*	Hepatocarcinoma 3924A cells	Dietary supplementation with EPA and DHA	Increased apoptosis and decreased proliferation	
	Normal spleen cells in culture with and without mitogens	n-3s in culture media	Decreased proliferation	
	Various cancerous as well as normal cell lines	n-3s in culture media	Decreased proliferation	

Table C.3.3. Non-systematic reviews of n-3 Fatty Acids and Differentiation.

Author, Year	Definition and Model(s)	Outcomes Measured	Conclusions	Years
Burns, 1994[108]	No definition provided HL-60 leukemia cells Cultured colon cancer cells	 Retinoic acid-mediated differentiation as measured by superoxide production and nitroblue tetrazolium reduction Butyrate-induced differentiation	 Plasma membrane PUFA appear to mediate differentiation of HL-60 cells in vitro: enrichment with DHA increases rate of differentiation and decreases growth rate cf. enrichment with oleic acid Differentiation facilitated by DHA	67-92
Avula, 2000[87]*	No definition provided Colon cancer cell EPA and DHA-mediated changes in proliferation	Proliferation, apoptosis, numbers of differentiating cells	EPA and DHA increase numbers of differentiating cells without modifying crypt morphology or cell number per crypt column	
Stoll, 2002[88]	No definition provided PPAR-γ is a nuclear receptor activated by PUFAs, antidiabetic agents that inhibit growth of cancer cells; HBC cells in culture	Expression of PPAR-γ and differentiation	n-3s increase PPAR-γ expression in nuclei of many cell types. Such activation has been shown to increase differentiation of HBC cells	

Appendix C. Evidence Tables (continued)

Table C.3.4. Non-systematic reviews of n-3 Fatty Acids and Apoptosis.

Author, Year	(Definition) and Model(s)	Outcomes	Conclusions	Years
Troyer, 1996[89]	(Apoptosis is an energy-dependent physiological process of cellular self-elimination) Proposes that n-3s could affect apoptosis and suggests several mechanisms: n-3s increase expression of free radical scavenging enzymes, which should maintain normal apoptosis.			14-95
	N-3 mediation of gene expression: HL-60 cells	EPA effects on proliferation and apoptosis	EPA inhibits proliferation and stimulates apoptosis FO suppresses H-ras expression	
	DMBA induced breast cancer cells	Effect of fish oil on H-ras expression		
Das, 1999[109]	(no definition) Variety of tumor cell models and normal cell lines	Effects of EFAs on apoptosis	In contrast to findings of others, both n-6s and n-3s appear to stimulate apoptosis	'84-'98
Johnson, 2002[90]	(Apoptosis is the selective destruction of individual cells dispersed throughout a tissue, characterized by, among other changes, shrinkage and convolution of the nucleus, chromatin aggregation, and loss of intercellular contact) Proposes that rapidly proliferating cells such as those in the intestinal mucosa are protected from tumorigenic mutational events by n-3-mediated apoptosis, independent of COX-2 inhibition.	Effects of LCPUFAs on intestinal apoptosis and aberrant crypt foci	Findings suggest apoptosis mediates anticarcinogenic effects of fish oil in small intestine, which in turn my be mediated by lipid peroxidation and intracellular redox potential	'92-'01
	Human colorectal adenocarcinoma cell line HT29	EPA leads to cellular detachment and apoptosis; enhanced by glutathione depletion/ blocked by antioxidants		
	Feeding rats fish oil followed by exposure to DMH	Fish oil feeding enhances apoptosis, decreases mitosis, and reduces ACF frequency in intestinal epithelial cells; enhanced by glutathione depletion		

Table C.3.4. Non-systematic reviews of n-3 Fatty Acids and Apoptosis.

Author, Year	(Definition) and Model(s)	Outcomes	Conclusions	Years
Avula, 2000[87]	(Apoptosis is synonymous with "programmed cell death" occurring at a specific time during development. Appears to result from induction of active intracellular processes.) Models: 1) n-3s susceptible to oxidative stress/peroxidation: a variety of cell culture systems Animals in feeding studies: fed high n-3 diets show increased n-3s in membrane lipids. Requires antioxidant supplementation to prevent peroxidation. However, high levels of antioxidants reduce peroxidation and increase tumor growth. 2) Transgenic and normal mice, HL-60 and K-562 cells in vitro: Bcl-2 is a gene product that suppresses apoptosis, a mechanism that plays a role in pathogenesis of some cancers; could be mechanism by which n-3s suppress tumor growth, i.e. stimulating apoptosis. Thus highly unsaturated FA are susceptible to peroxidation and these peroxides can induce apoptosis. 3) Fas/Apo-1, a TNF-family receptor. Fas-L, a ligand, mediates apoptosis by x-linking the Fas receptor. Splenocytes. Increasing evidence suggests that tumor progression can be controlled by altering cancer cell sensitivity to Fas-mediated apoptosis (w/ n-3s).	n-3 effects on apoptosis Membrane n-3 levels Bcl-2 expression Fas-L gene expression and apoptosis	n-3s increase apoptosis Increased by n-3 feeding Inhibited by n-3s in vivo and in vitro N-3s increase both Fas expression, apoptosis, and cell sensitivity to Fas-mediated apoptosis	'87-'99

Notes: HBC Human breast cancer; PPAR Peroxisome proliferator-activated receptor

Table C.3.5. Evidence for Role of Genes Involved in n-3 Metabolism and Transport.

Author, Year	Gene Product	Model	Outcomes	Years Cited
Blok, 1994[95]	Phospholipases, COX, and LO	Numerous rodent ex vivo models: role of n-3s in cytokine production	EPA rapidly incorporated into membrane phospholipids, replaces AA as substrate for COX etc., and is converted to less active PGE_3 and LTB_5; mimic effects of dual inhibition of COX and LO. Effects in mice opposite to those in humans, rats. Poss. due to different cell types studied.	'88-'94
Ma, 1996[93]*	COX-2 pathway	Unknown	n-3s inhibit oxidative metabolism of AA involved in PG synthesis and decreases PGE2 synthesis; indomethacin, a COX-2 inhibitor, inhibits colon carcinogenesis. MO increases lipid peroxidation in colon tumors	
Rose, 1997[98]	COX-2 and LO	Expt. mammary carcinogenesis; human breast cancer cell progression in nude mice	Suppressive effects of n-3s appear to be mediated by inhibition of conversion of AA to PGE2 and 12-HETE	'88, 95
Calder, 1997[96]	Phospholipases A2, C COX-2, LO	None: background info on role of n-3s in cytokine production	Precursor PUFAs released from membrane phospholipids by phospholipases: play role along with COX and LO in amounts and types of eicosanoids synthesized; EPA is substrate for COX and 5-LO	82-97
Rose, 2000[97]	LO and COX Phospholipase A2	Nude mouse/breast cancer cell lines model of angiogenesis potentiation by n-3s and n-6s Human colon cancer cells that overexpress COX-2	n-6 LO and COX metabolites (12-HETE and PGE2, resp.) are angiogenic in in vitro assays. Stimulate VEGF. Angiogenesis assoc. with tumor progression and poor prognosis. Inhibited by DHA and COX-2 inhibitor similarly. Result is stimulation of vascular endothelial cell migration and formation of capillary-like tubes in culture	'81-'99
Avula, 2000[87]*	Peroxidases (used here to include LO, COX)	Variety of cell culture systems; in vivo diet expt. in mice	PUFAs susceptible to lipid peroxidation. Oxidative stress induces apoptosis in cell culture; n-3 feeding associated with increased markers for generation of reactive oxygen species and increased apoptosis; supplementation with antioxidants inhibits this and increases tumor cell growth (as well as preserving immune cell fn). N-3s themselves stimulate antioxidant enzyme activities.	

* COX Cyclooxygenase; HETE Hydroxyeicosatetraenoic acid; LO Lipoxygenase; LTB Leukotriene B; PGE Prostaglandin E; VEGF Vascular endothelial growth factor; *Review included in Response to Question 1.3 on apoptosis.

Updated evidence table for prospective cohort studies of risk of different types of cancer for different categories of consumption of omega-3 FA, by category for each type of cancer. (updated October 2005)

Appendix D: Updated Evidence Table for Prospective Cohort Studies

The data in this report that pertain to the effects of omega-3 fatty acids on cancer incidence were updated in October 2005 using the same search strategy detailed in Appendix A but restricting to observational studies. As a result of that search, 311 additional titles were identified among which 18 met title inclusion criteria. Among these, 5 met the inclusion criteria for this report, i.e., they were prospective cohort studies that described the effect of omega-3 fatty acid consumption on the incidence of cancer in humans. In total, through October 2005, 38 prospective cohort studies were identified that described the effect of omega-3 fatty acids on the incidence of cancer.

The evidence table details the age- and multivariate-adjusted risk ratios that were reported for each study arm of each study. The table is ordered by cancer type. For each type of cancer the table is stratified by the specific categories of omega-3 fatty acids for which the risk ratios were reported, i.e. fish, total omega-3, marine omega-3, ALA, EPA or DHA.

A list of studies included in this analysis and a list of the studies that were reviewed but excluded follows the evidence table.

Updated evidence table for prospective cohort studies of risk of different types of cancer for different categories of consumption of omega-3 FA, by category for each type of cancer. (updated October 2005)

Cohort Author, Year	Study arm (quartile, quintile or dose group)	Median intake	Estimates of effect				Multivariate Adjustors
			Age adjusted RR (95% CI)		Multivariate RR (95% CI)		
Upper aerodigestive cancer							
FISH							
Honolulu Heart Program Chyou, 1995	1	< 1 g/wk	NR		1		Age, alcohol, number of cigarettes/d, number of years smoked.
	2	2-4 g/wk	NR		1.02	(0.65, 1.61)	
	3	≥ 5 g/wk	NR		1.37	(0.70, 2.69)	
	Total n = 7,995					p = 0.473‡	
Bladder cancer							
FISH							
Honolulu Heart Program Chyou, 1993	1	≤ 1 times/wk	NR		1		Age, smoking.
	2	2-4 times/wk	NR		0.90	(0.59, 1.39)	
	3	≥ 5 times/wk	NR		0.67	(0.26, 1.67)	
	Total n = 7,995					p = 0.377‡	
Breast cancer							
FISH							
Diet, Cancer and Health Study Stripp, 2003	1	0-26 g/d	1		1		Age, parity, number of births, age at first birth, BMI, benign breast tumor, years of school, use of HRT, duration of HRT use, alcohol.
	2	27-39 g/d	1.01	(0.77. 1.32)	0.99	(0.76, 1.30)	
	3	40-58 g/d	1.17	(0.89, 1.53)	1.12	(0.85, 1.47)	
	4	> 58 g/d	1.54	(1.18, 2.02)	1.47	(1.10, 1.98)	
	Total n = 23,693						

Updated evidence table for prospective cohort studies of risk of different types of cancer for different categories of consumption of omega-3 FA, by category for each type of cancer. (updated October 2005)

Cohort Author, Year		Study arm (quartile, quintile or dose group)	Median intake	Estimates of effect			Multivariate Adjustors
				Age adjusted RR (95% CI)	Multivariate RR (95% CI)		
Breast cancer (continued)							
FISH (continued)							
Life Span Study Key, 1999	Fish, not dry	1	≤ 1 times/wk	NR	1		Attained age, calendar period, city, age at time of bombing, and radiation dose.
		2	2 - 4 times/wk	NR	1.08	(0.84, 1.39)	
		3	≥ 5 times/wk	NR	1.17	(0.90, 1.54)	
		4	Unknown	NR	0.92	(0.66, 1.29)	
		Total n = 34,759				p = 0.21‡	
	Fish, dry	1	≤ 1 times/wk	NR	1		
		2	2 - 4 times/wk	NR	0.85	(0.64, 1.12)	
		3	≥ 5 times/wk	NR	0.49	(0.24, 1.02)	
		4	Unknown	NR	0.77	(0.60, 0.98)	
		Total n = 34,759				p = 0.03‡	
Norwegian National Health Screening Service Cohort Vatten, 1990 [40]		1	≤ 2 g/wk	1§	NR		NR
		2	≥ 2 g/wk	1.2§ (0.8, 1.7)	NR		
		Total n = 14,500		p = 0.24‡			
Nurses' Health Study Holmes, 1999 and 2003		1	≤ 0.13 serv/d	NR	1		Age, 2yr time period, Total n = energy, alcohol intake, parity and age at first birth, BMI at age 18, weight change since 18, height in inches, family history of breast cancer, history of benign breast disease, age at menarche in years, menopausal status, age at menopausal and HRT use, duration of menopausal.
		2	0.14-0.2 serv/d	NR	0.98	(0.89, 1.08)	
		3	0.21-0.27 serv/d	NR	0.97	(0.87, 1.08)	
		4	0.28-0.39 serv/d	NR	0.99	(0.90, 1.09)	
		5	≥ 0.4 serv/d	NR	1.04	(0.93, 1.14)	
		Total n = 88,647				p = 0.55‡	

Updated evidence table for prospective cohort studies of risk of different types of cancer for different categories of consumption of omega-3 FA, by category for each type of cancer. (updated October 2005)

Cohort Author, Year	Study arm (quartile, quintile or dose group)	Median intake	Estimates of effect		
			Age adjusted RR (95% CI)	Multivariate RR (95% CI)	Multivariate Adjustors
Breast cancer (continued)					
TOTAL OMEGA-3					
Nurses' Health Study Cho, 2003	1	0.03 % EI intake	1	1	Age, time enrolled, smoking, height, body mass index, total energy, protein, alcohol intake, parity and age at first birth, family history of breast cancer, history of benign breast disease, age at menarche in years, menopausal status, oral contraceptive use, duration of menopausal.
	2	0.05 % EI intake	0.94 (0.74, 1.19)	0.95 (0.74, 1.21)	
	3	0.08 % EI intake	0.91 (0.72, 1.15)	0.92 (0.72, 1.17)	
	4	0.12 % EI intake	1.06 (0.84, 1.33)	1.05 (0.82, 1.33)	
	5	0.19 % EI intake	1.01 (0.08, 1.27)	1.01 (0.78, 1.31)	
	Total n = 88,410		p = 0.43‡	p = 0.50‡	
Singapore Chinese Health Study Gago-Dominguez, 2003 [50]	1	NR	NR	1	Age at baseline interview, year of recruitment, dialect group, education, daily alcohol drinker, family history of breast cancer, age when period became regular, number of live births.
	2	NR	NR	0.82 (0.60, 1.1)	
	3	NR	NR	0.84 (0.62, 1.15)	
	4	NR	NR	0.87 (0.64, 1.18)	
	Total n = 35,298			p = 0.40‡	
Marine OMEGA-3					
Singapore Chinese Health Study Gago-Dominguez, 2003 [50]	1	NR	NR	1	Age at baseline interview, year of recruitment, dialect group, education, daily alcohol drinker, family history of breast cancer, age when period became regular, number of live births.
	2	NR	NR	0.75 (0.55, 1.01)	
	3	NR	NR	0.75 (0.55, 1.02)	
	4	NR	NR	0.72 (0.53, 0.98)	
	Total n = 35,298			p = 0.40‡	

Updated evidence table for prospective cohort studies of risk of different types of cancer for different categories of consumption of omega-3 FA, by category for each type of cancer. (updated October 2005)

Cohort Author, Year	Study arm (quartile, quintile or dose group)	Median intake	Estimates of effect		
			Age adjusted RR (95% CI)	Multivariate RR (95% CI)	Multivariate Adjustors
Breast cancer (continued)					
ALA					
Netherlands Cohort Study Voorrips, 2002	1	0.6	1	1	Age, history of benign breast cancer, breast cancer in one or more sisters, age at menarche, age at menopause, oral contraceptive use, parity, age at first childbirth, Quetelet index, education, alcohol use, current cigarette smoking, total energy intake, total energy-adjusted fat intake.
	2	0.8	0.76 (0.58, 1.00)	0.78 (0.57, 1.05)	
	3	1.0	0.92 (0.71, 1.20)	1.03 (0.76, 1.39)	
	4	1.3	0.69 (0.52, 0.91)	0.74 (0.54, 1.00)	
	5	1.7	0.68 (0.51, 0.91)	0.70 (0.51, 0.97)	
	Total n = 62,573		p = 0.001‡	p = 0.006‡	
EPA					
Netherlands Cohort Study Voorrips, 2002	1	0 g/d	1	1	Age, history of benign breast cancer, breast cancer in one or more sisters, age at menarche, age at menopause, oral contraceptive use, parity, age at first childbirth, Quetelet index, education, alcohol use, current cigarette smoking, total energy intake, total energy-adjusted fat intake.
	2	0.01 g/d	1.18 (0.88, 1.56)	1.15 (0.84, 1.58)	
	3	0.02 g/d	1.14 (0.87, 1.50)	1.10 (0.82, 1.49)	
	4	0.04 g/d	1.23 (0.93, 1.62)	1.22 (0.90, 1.65)	
	5	0.08 g/d	1.03 (0.78, 1.37)	0.98 (0.72, 1.35)	
	Total n = 62,573		p = 0.63‡	p = 0.87‡	
DHA					
Netherlands Cohort Study Voorrips, 2002	1	0.01 g/d	1	1	Age, history of benign breast cancer, breast cancer in one or more sisters, age at menarche, age at menopause, oral contraceptive use, parity, age at first childbirth, Quetelet index, education, alcohol use, current cigarette smoking, total energy intake, total energy-adjusted fat intake.
	2	0.03 g/d	1.11 (0.83, 1.47)	1.10 (0.81, 1.51)	
	3	0.05 g/d	1.04 (0.78, 1.37)	1.03 (0.76, 1.40)	
	4	0.08 g/d	1.20 (0.91, 1.58)	1.21 (0.90, 1.64)	
	5	0.14 g/d	1.02 (0.77, 1.36)	1.00 (0.72, 1.37)	
	Total n = 62,573		p = 0.62‡	p = 0.70‡	

Updated evidence table for prospective cohort studies of risk of different types of cancer for different categories of consumption of omega-3 FA, by category for each type of cancer. (updated October 2005)

Cohort Author, Year	Study arm (quartile, quintile or dose group)	Median intake	Estimates of effect		
			Age adjusted RR (95% CI)	Multivariate RR (95% CI)	Multivariate Adjustors
Colorectal cancer					
FISH					
Health Professionals Follow-up Study Giovannucci, 1994	1	8.4 g/d	1	NR	NR
	2	20.9 g/d	0.85 (0.54, 1.33)	NR	
	3	31.0 g/d	1.05 (0.68, 1.61)	NR	
	4	47.8 g/d	0.80 (0.51, 1.26)	NR	
	5	83.4 g/d	1.06 (0.70, 1.60)	NR	
	Total n = 47,949		p = 0.79‡		
Netherlands Cohort Study Goldbohm, 1994	1	0 g/d	NR	1	Age and energy.
	2	0-10 g/d	NR	1 (0.68, 1.47)	
	3	10-20 g/d	NR	0.74 (0.48, 1.15)	
	4	> 20 g/d	NR	0.81 (0.56, 1.17)	
	Total n = 3,111			p = 0.14‡	
Nurses' Health Study Willett, 1990	1	< 1 g/m	1	NR	NR
	2	1-3 g/m	1.29 (0.70, 2.40)	NR	
	3	1 g/wk	0.92 (0.49, 1.72)	NR	
	4	2-4 g/wk	0.75 (0.35, 1.58)	NR	
	5	4 g/wk	1.06 (0.36, 3.12)	NR	
	Total n = 88,751		p = 0.09‡		
New York University Women's Health Study Kato, 1997	1	NR	NR	1	Age, total calorie, place at enrollment and highest level of education.
	2	NR	NR	1.01 (0.62, 1.67)	
	3	NR	NR	0.65 (0.37, 1.13)	
	4	NR	NR	0.49 (0.27, 0.89)	
	Total n = 14,727			p = 0.007‡	

Updated evidence table for prospective cohort studies of risk of different types of cancer for different categories of consumption of omega-3 FA, by category for each type of cancer. (updated October 2005)

Cohort Author, Year		Study arm (quartile, quintile or dose group)	Median intake	Estimates of effect			Multivariate Adjustors
				Age adjusted RR (95% CI)	Multivariate RR (95% CI)		
Colorectal cancer (continued)							
FISH (continued)							
Swedish women in mammography -screening program Larsson,2005	Colorectal	1	0.5 serv/wk	NR	1		Age, BMI, education level, energy intake, intake of alcohol, calcium, folic acid, saturated fat, fruits, vegetables and whole grains.
		2	0.5-<1.0 serv/wk	NR	0.94	(0.72, 1.22)	
		3	1.0-<2.0 serv/wk	NR	1.21	(0.94, 1.55)	
		4	≥2 serv/wk	NR	1.08	(0.81, 1.43)	
		Total n = 61,433				p = 0.48‡	
	Proximal Colon	1	0.5 serv/wk	NR	1		
		2	0.5-<1.0 serv/wk	NR	0.88	(0.57, 1.36)	
		3	1.0-<2.0 serv/wk	NR	1.13	(0.75, 1.71)	
		4	≥2 serv/wk	NR	1.03	(0.63, 1.67)	
		Total n = 61,433				p = 0.70‡	
	Distal Colon	1	0.5 serv/wk	NR	1		
		2	0.5-<1.0 serv/wk	NR	0.79	(0.46, 1.35)	
		3	1.0-<2.0 serv/wk	NR	0.92	(0.55, 1.52)	
		4	≥2 serv/wk	NR	0.83	(0.45, 1.51)	
		Total n = 61,433				p = 0.55‡	
	Rectum	1	0.5 serv/wk	NR	1		
		2	0.5-<1.0 serv/wk	NR	1.11	(0.68, 1.81)	
		3	1.0-<2.0 serv/wk	NR	1.32	(0.83, 2.11)	
		4	≥2 serv/wk	NR	1.08	(0.63, 1.86)	
		Total n = 61,433				p = 0.97‡	

Updated evidence table for prospective cohort studies of risk of different types of cancer for different categories of consumption of omega-3 FA, by category for each type of cancer. (updated October 2005)

Cohort Author, Year		Study arm (quartile, quintile or dose group)	Median intake	Estimates of effect				Multivariate Adjustors
				Age adjusted RR (95% CI)		Multivariate RR (95% CI)		
Colorectal cancer (continued)								
TOTAL OMEGA-3								
Iowa Women's Health Study Bostick, 1994		1	< 0.03 g/d	1		1		Age, total energy intake, height, parity, total vitamin E, a total vitamin E by age interaction term, vitamin A supplement intake.
		2	0.03-0.05 g/d	0.67	NR	0.82	(0.55, 1.24)	
		3	0.06-0.10 g/d	0.61	NR	0.77	(0.50, 1.17)	
		4	0.11-0.18 g/d	0.72	NR	0.96	(0.64, 1.43)	
		5	> 0.18 g/d	0.60	NR	0.70	(0.45, 1.09)	
		Total n = 35,215		p = 0.04‡		p = 0.26‡		
Women's Health Study Lin, 2004		1	NR	NR		1		Age, random treatment assignment, body mass index, family history of colorectal cancer, history of colorectal polyps, physical activity, cigarette smoking, alcohol consumption, postmenopausal hormone therapy, total energy intake.
		2	NR	NR	NR	0.88	(0.56, 1.37)	
		3	NR	NR	NR	0.89	(0.57, 1.39)	
		4	NR	NR	NR	0.92	(0.59, 1.43)	
		5	NR	NR	NR	1.11	(0.73, 1.69)	
		Total n = 37,547				p = 0.43‡		
MARINE OMEGA-3								
Nurses' Health Study Oh, 2005	Adenoma	1	0.03 % EI	1		1		Age, body mass index, smoking, alcohol intake, family history of colon cancer, history of previous endoscopic screening, aspirin use, physical activity, menopausal status and hormone use, energy, total fiber, red meat, calcium, folate, methionine, vitamin D, and *n*-6 fatty acid intake.
		2	0.05 % EI	1.02	(0.87, 1.20)	1.01	(0.86, 1.19)	
		3	0.08 % EI	0.97	(0.83, 1.14)	0.97	(0.81, 1.15)	
		4	0.11 % EI	1.02	(0.87, 1.19)	1.05	(0.87, 1.26)	
		5	0.18 % EI	0.98	(0.84, 1.14)	1.04	(0.84, 1.27)	
		Total n = 1,719			p = 0.73‡		p = 0.66‡	

Updated evidence table for prospective cohort studies of risk of different types of cancer for different categories of consumption of omega-3 FA, by category for each type of cancer. (updated October 2005)

Cohort Author, Year		Study arm (quartile, quintile or dose group)	Median intake	Estimates of effect				Multivariate Adjustors
				Age adjusted RR (95% CI)		Multivariate RR (95% CI)		
Colorectal cancer (continued)								
MARINE OMEGA-3 (continued)								
Nurses' Health Study Oh, 2005	Large Bowel	1	0.03 % EI	1		1		Age, body mass index, smoking, alcohol intake, family history of colon cancer, history of previous endoscopic screening, aspirin use, physical activity, menopausal status and hormone use, energy, total fiber, red meat, calcium, folate, methionine, vitamin D, and *n*-6 fatty acid intake.
		2	0.05 % EI	0.81	(0.64, 1.02)	0.82	(0.64, 1.04)	
		3	0.08 % EI	0.77	(0.61, 0.97)	0.78	(0.61, 1.01)	
		4	0.11 % EI	0.76	(0.61, 0.96)	0.81	(0.62, 1.06)	
		5	0.18 % EI	0.69	(0.55, 0.87)	0.74	(0.54, 1.01)	
		Total n = 705			p = 0.01‡		p = 0.16‡	
	Small Bowel	1	0.03 % EI	1		1		
		2	0.05 % EI	1.27	(1.01, 1.59)	1.23	(0.97, 1.55)	
		3	0.08 % EI	1.22	(0.97, 1.54)	1.18	(0.92, 1.51)	
		4	0.11 % EI	1.30	(1.04, 1.63)	1.30	(1.00, 1.67)	
		5	0.18 % EI	1.31	(1.05, 1.63)	1.36	(1.02, 1.81)	
		Total n = 897			p = 0.07‡		p = 0.09‡	
	Distal Colon	1	0.03 % EI	1		1		
		2	0.05 % EI	0.99	(0.82, 1.19)	0.97	(0.80, 1.17)	
		3	0.08 % EI	0.94	(0.78, 1.13)	0.92	(0.75, 1.12)	
		4	0.11 % EI	1.02	(0.86, 1.23)	1.03	(0.83, 1.27)	
		5	0.18 % EI	1.01	(0.84, 1.21)	1.04	(0.82, 1.31)	
		Total n = 1,280			p = 0.76‡		p = 0.51‡	
	Rectum	1	0.03 % EI	1		1		
		2	0.05 % EI	1.18	(0.89, 1.57)	1.19	(0.88, 1.60)	
		3	0.08 % EI	1.10	(0.82, 1.47)	1.13	(0.83, 1.55)	
		4	0.11 % EI	1.08	(0.81, 1.44)	1.16	(0.83, 1.62)	
		5	0.18 % EI	0.99	(0.74, 1.32)	1.11	(0.76, 1.62)	
		Total n = 505			p = 0.05‡		p = 0.91‡	

Updated evidence table for prospective cohort studies of risk of different types of cancer for different categories of consumption of omega-3 FA, by category for each type of cancer. (updated October 2005)

Cohort Author, Year		Study arm (quartile, quintile or dose group)	Median intake	Estimates of effect			Multivariate Adjustors
				Age adjusted RR (95% CI)	Multivariate RR (95% CI)		
Colorectal cancer (continued)							
ALA							
Swedish women in mammography-screening program Terry, 2001	Colon	1	0.45 g/d	NR	1		Age, BMI, education level, energy intake, intakes of red meat and alcohol, energy, dietary fiber, calcium, vitamin C, folic acid, Vitamin D, saturated fat, monounsaturated fat, polyunsaturated fat.
		2	0.50 g/d	NR	0.96	(0.68, 1.35)	
		3	0.54 g/d	NR	0.96	(0.67, 1.37)	
		4	0.70 g/d	NR	0.90	(0.63, 1.28)	
		Total n = 61,463				p = 0.57‡	
	Colorectal	1	0.45 g/d	NR	1		
		2	0.50 g/d	NR	0.96	(0.73, 1.27)	
		3	0.54 g/d	NR	0.96	(0.72, 1.28)	
		4	0.70 g/d	NR	0.99	(0.75, 1.32)	
		Total n = 61,463				p = 0.99‡	
	Rectal	1	0.45 g/d	NR	1		
		2	0.50 g/d	NR	0.95	(0.60, 1.52)	
		3	0.54 g/d	NR	0.92	(0.56, 1.49)	
		4	0.70 g/d	NR	1.11	(0.70, 1.78)	
		Total n = 61,463				p = 0.65‡	

Updated evidence table for prospective cohort studies of risk of different types of cancer for different categories of consumption of omega-3 FA, by category for each type of cancer. (updated October 2005)

Cohort Author, Year		Study arm (quartile, quintile or dose group)	Median intake	Estimates of effect			Multivariate Adjustors
				Age adjusted RR (95% CI)	Multivariate RR (95% CI)		
Colorectal cancer (continued)							
EPA							
Swedish women in mammography-screening program Terry, 2001	Colon	1	0.03 g/d	NR	1		Age, BMI, education level, energy intake, intakes of red meat and alcohol, energy, dietary fiber, calcium, vitamin C, folic acid, Vitamin D, saturated fat, monounsaturated fat, polyunsaturated fat.
		2	0.05 g/d	NR	0.76	(0.54, 1.06)	
		3	0.07 g/d	NR	0.81	(0.58, 1.15)	
		4	0.09 g/d	NR	0.85	(0.60, 1.21)	
		Total n = 61,463				p = 0.46‡	
	Colorectal	1	0.03 g/d	NR	1		
		2	0.05 g/d	NR	0.80	(0.68, 1.15)	
		3	0.07 g/d	NR	0.96	(0.73, 1.26)	
		4	0.09 g/d	NR	0.96	(0.72, 1.28)	
		Total n = 61,463				p = 0.91‡	
	Rectal	1	0.03 g/d	NR	1		
		2	0.05 g/d	NR	1.17	(0.75, 1.83)	
		3	0.07 g/d	NR	1.29	(0.80, 2.06)	
		4	0.09 g/d	NR	1.25	(0.75, 2.06)	
		Total n = 61,463				p = 0.35‡	

Updated evidence table for prospective cohort studies of risk of different types of cancer for different categories of consumption of omega-3 FA, by category for each type of cancer. (updated October 2005)

Cohort Author, Year		Study arm (quartile, quintile or dose group)	Median intake	Estimates of effect			Multivariate Adjustors
				Age adjusted RR (95% CI)	Multivariate RR (95% CI)		
Colorectal cancer (continued)							
DHA							
Swedish women in mammography-screening program Terry, 2001	Colorectal	1	0.08 g/d	NR	1		Age, BMI, education level, energy intake, intakes of red meat and alcohol, energy, dietary fiber, calcium, vitamin C, folic acid, Vitamin D, saturated fat, monounsaturated fat, polyunsaturated fat. p = 0.52‡
		2	0.11 g/d	NR	0.88	(0.67, 1.15)	
		3	0.13 g/d	NR	0.87	(0.66, 1.15)	
		4	0.18 g/d	NR	0.90	(0.67, 1.20)	
		Total n = 61,463				p = 0.49‡	
	Colon	1	0.08 g/d	NR	1		
		2	0.11 g/d	NR	0.84	(0.60, 1.17)	
		3	0.13 g/d	NR	0.74	(0.51, 1.06)	
		4	0.18 g/d	NR	0.88	(0.61, 1.26)	
		Total n = 61,463				p = 0.41‡	
	Rectal	1	0.08 g/d	NR	1		
		2	0.11 g/d	NR	1.03	(0.66, 1.61)	
		3	0.13 g/d	NR	1.16	(0.73, 1.8)	
		4	0.18 g/d	NR	1.03	(0.62, 1.71)	
		Total n = 61,463				p = 0.79‡	

Updated evidence table for prospective cohort studies of risk of different types of cancer for different categories of consumption of omega-3 FA, by category for each type of cancer. (updated October 2005)

Cohort Author, Year		Study arm (quartile, quintile or dose group)	Median intake	Estimates of effect			
				Age adjusted RR (95% CI)	Multivariate RR (95% CI)		Multivariate Adjustors
Lung cancer							
FISH							
Aichi Prefecture Cohort, Japan Takezaki, 2003		1	< 1 times/wk	NR	1		Age, sex, smoke, occupation.
		2	1-2 times/wk	NR	0.99	(0.48, 2.03)	
		3	≥ 3 times/wk	NR	0.32	(0.13, 0.76)	
		Total n = 5,885				p = 0.003‡	
Japan Collaborative Cohort Ozasa, 2001	Men	1	≤ 1-2 times/wk	NR	1§		Age, parent's history of lung cancer, smoking status, smoking index and time since quitting smoking.
		2	3-4 times/wk	NR	1.12§	(0.87, 1.43)	
		3	almost every d	NR	1.03§	(0.79, 1.34)	
		Total n = 42,940				p = 0.72‡	
	Women	1	≤ 1-2 times/wk	NR	1		
		2	3-4 times/wk	NR	0.73	(0.45, 1.21)	
		3	almost every d	NR	0.88	(0.52, 1.49)	
		Total n = 55,308				p = 0.50‡	
Norwegian Cohorts Kvale, 1983	Histologic verification	1	< 10 times/m	NR	1		Age, cigarette smoking, region and urban/rural place of residence.
		2	10-14 times/m	NR	NR		
		3	15-19 times/m	NR	NR		
		4	≥ 20 times/m	NR	0.82	NR	
		Total n = 13785				p = 0.63‡	
	Squamous and small-	1	< 10 times/m	NR	1		
		2	10-14 times/m	NR	NR		
		3	15-19 times/m	NR	NR		
		4	≥ 20 times/m	NR	0.98	NR	
		Total n = 13785				p = 0.99‡	
Norwegian National Health Screening Service Cohort Veierod, 1997		1	<1 times/wk		1§		Smoking status, gender, age at inclusion, attained age.
		2	1-2 times/wk		1.1‖	(0.6, 2.2)	
		3	3-4 times/wk		1.0‖	(0.5, 2.1)	
		4	≥ 5 times/wk		3.0‖	(1.2, 7.3)	
		Total n = 51,452				p = 0.2‡	

Updated evidence table for prospective cohort studies of risk of different types of cancer for different categories of consumption of omega-3 FA, by category for each type of cancer. (updated October 2005)

Cohort Author, Year	Study arm (quartile, quintile or dose group)	Median intake	Estimates of effect		
			Age adjusted RR (95% CI)	Multivariate RR (95% CI)	Multivariate Adjustors
Non-Hodgkin's lymphoma					
FISH					
Iowa Women's Health Study Chiu, 1996	1	< 4 serv/m	NR	1	Age and energy.
	2	4-6 serv/m	NR	0.94 (0.59, 1.49)	
	3	> 6 serv/m	NR	0.81 (0.49, 1.35)	
	Total n = 35,156			p = 0.42‡	
Omega-3					
Nurses' Health Study Zhang, 1999	1	0.02 % EI intake	1	1	Age, total energy, length of follow-up, geographic region, cigarette smoke, height in inches, saturated and trans unsaturated fats, fruit, vegetable intake.
	2	0.03 % EI intake	1.2 NR	1.2 NR	
	3	0.04 % EI intake	1.3 NR	1.4 NR	
	4	0.05 % EI intake	1.1 NR	1.2 NR	
	5	0.10 % EI intake	1.1 (0.7, 1.7)	1.4 (0.8, 2.2)	
	Total n = 88,410		p = 0.90‡	Testing NR	
Ovarian cancer					
FISH					
Swedish Mammography Cohort Larsson, 2005	1	< 1 serv/wk	1.00	1.0	Age, body mass index, education level, parity, oral contraceptive use, postmenopausal hormone use, total energy intake, consumption of fruits, vegetables and dairy products..
	2	1.0 - <2.0 serv/wk	1.03 (0.77, 1.39)	1.08 (0.79, 1.46)	
	3	2.0 - <3.0 serv/wk	1.02 (0.71, 1.48)	0.80 (0.71, 1.52)	
	4	>= 3 serv/wk	1.01 (1.01, 1.41)	0.82 (0.75, 1.55)	
	Total n = 61,057		p = 0.97	p = 0.69‡	

Updated evidence table for prospective cohort studies of risk of different types of cancer for different categories of consumption of omega-3 FA, by category for each type of cancer. (updated October 2005)

Cohort Author, Year	Study arm (quartile, quintile or dose group)	Median intake	Estimates of effect		
			Age adjusted RR (95% CI)	Multivariate RR (95% CI)	Multivariate Adjustors
Ovarian cancer (continued)					
ALA					
Nurses' Health Study Bertone, 2002	1	NR	1	1	Age, parity, age at menarche, oral contraceptive use and duration, menopausal status/postmenopausal hormone use, smoking status.
	2	NR	0.74 NR	0.75 (0.53, 1.08)	
	3	NR	0.62 NR	0.64 (0.44, 0.94)	
	4	NR	0.86 NR	0.88 (0.63, 1.24)	
	5	NR	0.98 NR	1.00 (0.72, 1.39)	
	Total n = 80,258			p = 0.72‡	
EPA					
Nurses' Health Study Bertone, 2002	1	NR	1	1	Age, parity, age at menarche, oral contraceptive use and duration, menopausal status/postmenopausal hormone use, smoking status.
	2	NR	1.01 NR	1.04 (0.68, 1.59)	
	3	NR	0.73 NR	0.75 (0.47, 1.17)	
	4	NR	0.96 NR	1.00 (0.66, 1.52)	
	5	NR	0.96 NR	0.97 (0.64, 1.48)	
	Total n = 80,258			p = 0.80‡	
DHA					
Nurses' Health Study Bertone, 2002	1	NR	1	1	Age, parity, age at menarche, oral contraceptive use and duration, menopausal status/postmenopausal hormone use, smoking status.
	2	NR	1.06 NR	1.06 (0.70, 1.61)	
	3	NR	0.67 NR	0.67 (0.42, 1.08)	
	4	NR	1.05 NR	1.07 (0.71, 1.63)	
	5	NR	0.88 NR	0.86 (0.55, 1.33)	
	Total n = 80,258			p = 0.52‡	

Updated evidence table for prospective cohort studies of risk of different types of cancer for different categories of consumption of omega-3 FA, by category for each type of cancer. (updated October 2005)

Cohort Author, Year	Study arm (quartile, quintile or dose group)	Median intake	Estimates of effect		
			Age adjusted RR (95% CI)	Multivariate RR (95% CI)	Multivariate Adjustors
Pancreatic cancer					
FISH					
Alpha-tocopherol, Beta-Carotene Cancer Prevention Study Stolzenberg-Solomon, 2002	1	NR	NR	1	Energy intake by the residual method, age, and years of smoking, energy-adjusted saturated fat intake.
	2	NR	NR	1.22 (0.75, 1.97)	
	3	NR	NR	1.14 (0.70, 1.86)	
	4	NR	NR	1.07 (0.65, 1.76)	
	5	NR	NR	0.91 (0.54, 1.52)	
	Total n = 27,111			p = 0.59‡	
TOTAL OMEGA-3					
Alpha-tocopherol, Beta-Carotene Cancer Prevention Study Stolzenberg-Solomon, 2002	1	NR	NR	1	Energy intake by the residual method, age, and years of smoking.
	2	NR	NR	0.97 (0.60, 1.60)	
	3	NR	NR	1.04 (0.64, 1.69)	
	4	NR	NR	1.16 (0.72, 1.86)	
	5	NR	NR	0.96 (0.58, 1.58)	
	Total n = 27,111			p = 0.90‡	
ALA					
Alpha-tocopherol, Beta-Carotene Cancer Prevention Study Stolzenberg-Solomon, 2002	1	NR	NR	1	Energy intake by the residual method, age, and years of smoking, energy-adjusted saturated fat intake.
	2	NR	NR	1.09 (0.69, 1.73)	
	3	NR	NR	1.10 (0.68, 1.79)	
	4	NR	NR	1.04 (0.61, 1.77)	
	5	NR	NR	1.11 (0.65, 1.91)	
	Total n = 27,111			p = 0.77‡	
Nurses' Health Study Michaud, 2003	1	0.7 g/d	1	1	Pack-years of smoking, BMI, history of diabetes mellitus, caloric intake, height, physical activity, menopausal status, glycemic load intake.
	2	0.8 g/d	1.03	1.08 (0.70, 1.67)	
	3	0.9 g/d	1	1.03 (0.66, 1.61)	
	4	1.0 g/d	0.75	0.80 (0.49, 1.30)	
	5	1.1 g/d	0.76	0.77 (0.47, 1.26)	
	Total n = 88,802		p = 0.12‡	p = 0.16‡	

Updated evidence table for prospective cohort studies of risk of different types of cancer for different categories of consumption of omega-3 FA, by category for each type of cancer. (updated October 2005)

Cohort Author, Year	Study arm (quartile, quintile or dose group)	Median intake	Estimates of effect		
			Age adjusted RR (95% CI)	Multivariate RR (95% CI)	Multivariate Adjustors
Prostate cancer					
FISH					
Hawaii Health Surveillance Program LeMarchand, 1994	1	NR	NR	1	Age, race, income.
	2	NR	NR	1.1 (0.7, 1.7)	
	3	NR	NR	0.9 (0.6, 1.3)	
	4	NR	NR	1.2 (0.8, 1.8)	
	Total n = 8,881			p = 0.55‡	
Health Professionals Follow-up Study Augustsson, 2003	1	< 2 times/m	1	1	Age, calories, fatty acid, lycopene, retinol, vitamin D and physical activity.
	2	2 times/m-1 time/wk	1.06 (0.92, 1.22)	1.05 (0.91, 1.21)	
	3	2-3 times/wk	1.06 (0.94, 1.20)	1.06 (0.93, 1.20)	
	4	> 3 times/wk	0.91 (0.79, 1.05)	0.93 (0.80, 1.08)	
	Total n = 47,882				
Seventh-day Adventist Mills, 1989	1	Never	1	NR	NR
	2	< 1 g/wk	1.68 (1.16, 2.43)	NR	
	3	≥ 1 g/wk	1.47 (0.84, 2.60)	NR	
	Total n = 14,000		p = 0.03‡		
Swedish Twin Registry Terry, 2001	1	Never/ seldom	1.7 (1.0, 3.0)	2.3 (1.2, 4.5)	Age, BMI, physical activity, smoking, consumption of alcohol, red meat, processed meat, fruit, vegetable and milk.
	2	Small	1.1 (0.9, 1.3)	1.2 (1.0, 1.4)	
	3	Moderate	1	1	
	4	Large	1.1 (0.8, 1.5)	1.0 (0.7, 1.6)	
	Total n = 6,272		p = 0.35‡	p = 0.05‡	

Updated evidence table for prospective cohort studies of risk of different types of cancer for different categories of consumption of omega-3 FA, by category for each type of cancer. (updated October 2005)

Cohort Author, Year	Study arm (quartile, quintile or dose group)	Median intake	Estimates of effect		Multivariate Adjustors
			Age adjusted RR (95% CI)	Multivariate RR (95% CI)	
Prostate cancer (continued)					
MARINE OMEGA-3					
Health Professionals Follow-up Study Giovannucci, 1993	1	0.05 g/d	1	NR	NR
	2	0.12 g/d	1.34 (0.78, 2.30)	NR	
	3	0.21 g/d	1.05 (0.59, 1.89)	NR	
	4	0.30 g/d	0.92 (0.51, 1.65)	NR	
	5	0.55 g/d	0.90 (0.51, 1.61)	NR	
	Total n = 47,855		p = 0.30‡		
ALA					
Health Professionals Follow-up Study Leitzmann, 2004§ Prostate cancer excluding stage A-1	1	<0.37% EI	1.0	1.0	Age, time period, major ancestry, family history of prostate cancer, BMI at age 21, height, type 2 diabetes, vasectomy, cigarettes in past decade, vigorous physical activity, intake of total energy, % energy from protein, % energy from monounsaturated fat, % energy from saturated fat, % energy from *trans* unsaturated fats, and intakes of calcium, supplemental vitamin E and lycopene.
	2	0.37-0.43% EI	1.08 NR	1.04 (0.89, 1.22)	
	3	0.44-0.49% EI	1.12 NR	1.05 (0.89, 1.25)	
	4	0.50-0.58% EI	1.24 NR	1.16 (0.97, 1.39)	
	5	>0.58% EI	1.11 NR	1.04 (0.85, 1.27)	
	Total n = 47,866		p = 0.10†	p = 0.10†	
Health Professionals Follow-up Study Leitzmann, 2004§ Advanced prostate cancer	1	<0.37% EI	1.0	1.0	
	2	0.37-0.43% EI	1.33 NR	1.47 (1.07, 2.01)	
	3	0.44-0.49% EI	1.41 NR	1.57 (1.12, 2.21)	
	4	0.50-0.58% EI	1.53 NR	1.77 (1.24, 2.53)	
	5	>0.58% EI	1.69 NR	1.98 (1.34, 2.93)	
	Total n = 47,866		p = 0.0005‡	p = 0.0005†	

* NR = Not Reported; ‡ = test for trend.

Updated evidence table for prospective cohort studies of risk of different types of cancer for different categories of consumption of omega-3 FA, by category for each type of cancer. (updated October 2005)

Cohort Author, Year	Study arm (quartile, quintile or dose group)	Median intake	Estimates of effect		
			Age adjusted RR (95% CI)	Multivariate RR (95% CI)	Multivariate Adjustors
Prostate cancer (continued)					
ALA (continued)					
Netherlands Cohort Study Schuurman, 1999	1	0.7 g/d	1	1	Age, family history of prostate carcinoma, socioeconomic status, total energy intake, total energy-adjusted fat intake.
	2	1.1 g/d	0.80 (0.59, 1..08)	0.76 (0.55, 1.05)	
	3	1.3 g/d	0.82 (0.61, 1.11)	0.82 (0.60, 1.13)	
	4	1.7 g/d	0.80 (0.59, 1.08)	0.80 (0.59, 1.10)	
	5	2.1 g/d	0.76 (0.56, 1.03)	0.76 (0.66, 1.04)	
	Total n = 58,279		p = 0.04‡	p = 0.09‡	
EPA					
Health Professionals Follow-up Study Leitzmann, 2004 Prostate cancer excluding stage A-1	1	<0.014% EI	1.0	1.0	Age, time period, major ancestry, family history of prostate cancer, BMI at age 21, height, type 2 diabetes, vasectomy, cigarettes in past decade, vigorous physical activity, intake of total energy, % energy from protein, % energy from monounsaturated fat, % energy from saturated fat, % energy from *trans* unsaturated fats, and intakes of calcium, supplemental vitamin E and lycopene.
	2	0.014-0.027% EI	1.14 NR	1.09 (0.93, 1.28)	
	3	0.028-0.042% EI	1.06 NR	1.02 (0.87, 1.21)	
	4	0.043-0.066% EI	1.03 NR	0.97 (0.81, 1.15)	
	5	>0.066% EI	0.92 NR	0.87 (0.72, 1.06)	
	Total n = 47,866		p = 0.04†	p = 0.03†	
Health Professionals Follow-up Study Leitzmann, 2004 Advanced prostate cancer	1	<0.014% EI	1.0	1.0	
	2	0.014-0.027% EI	1.01 NR	1.05 (0.75, 1.37)	
	3	0.028-0.042% EI	1.03 NR	0.99 (0.73, 1.35)	
	4	0.043-0.066% EI	0.89 NR	0.87 (0.63, 1.21)	
	5	>0.066% EI	0.82 NR	0.82 (0.58, 1.17)	
	Total n = 47,866		p = 0.08†	p = 0.18†	

* NR = Not Reported; ‡ = test for trend.

Updated evidence table for prospective cohort studies of risk of different types of cancer for different categories of consumption of omega-3 FA, by category for each type of cancer. (updated October 2005)

Cohort Author, Year	Study arm (quartile, quintile or dose group)	Median intake	Estimates of effect		
			Age adjusted RR (95% CI)	Multivariate RR (95% CI)	Multivariate Adjustors
Prostate cancer (continued)					
EPA (continued)					
Netherlands Cohort Study Schuurman, 1999	1	0 g/d	1	1	Age, family history of prostate carcinoma, socioeconomic status, total energy intake, total energy-adjusted fat intake.
	2	0.01 g/d	0.69 (0.50, 0.95)	0.66 (0.47, 0.91)	
	3	0.03 g/d	0.94 (0.69, 1.28)	0.92 (0.67, 1.27)	
	4	0.05 g/d	1.06 (0.79, 1.46)	1.05 (0.77, 1.44)	
	5	0.10 g/d	1.01 (0.75, 1.37)	1.00 (0.73, 1.35)	
	Total n = 58,279		p = 0.11‡	p = 0.10‡	
DHA					
Health Professionals Follow-up Study Leitzmann, 2004 Prostate cancer excluding stage A-1	1	<0.032% EI	1.0	1.0	Age, time period, major ancestry, family history of prostate cancer, BMI at age 21, height, type 2 diabetes, vasectomy, cigarettes in past decade, vigorous physical activity, intake of total energy, % energy from protein, % energy from monounsaturated fat, % energy from saturated fat, % energy from *trans* unsaturated fats, and intakes of calcium, supplemental vitamin E and lycopene.
	2	0.032-0.053% EI	1.16 NR	1.13 (0.96, 1.33)	
	3	0.054-0.079% EI	1.03 NR	0.99 (0.83, 1.17)	
	4	0.080-0.122% EI	1.03 NR	0.99 (0.83, 1.19)	
	5	>0.122% EI	1.03 NR	1.02 (0.84, 1.25)	
	Total n = 47,866		p = 0.63†	p = 0.77†	
Health Professionals Follow-up Study Leitzmann, 2004 Advanced prostate cancer	1	<0.032% EI	1.0	1.0	
	2	0.032-0.053% EI	0.84 NR	0.79 (0.58, 1.07)	
	3	0.054-0.079% EI	0.91 NR	0.84 (0.62, 1.15)	
	4	0.080-0.122% EI	0.86 NR	0.82 (0.59, 1.13)	
	5	>0.122% EI	0.73 NR	0.71 (0.49, 1.08)	
	Total n = 47,866		p = 0.06†	p = 0.13†	

Updated evidence table for prospective cohort studies of risk of different types of cancer for different categories of consumption of omega-3 FA, by category for each type of cancer. (updated October 2005)

Cohort Author, Year	Study arm (quartile, quintile or dose group)	Median intake	Estimates of effect		
			Age adjusted RR (95% CI)	Multivariate RR (95% CI)	Multivariate Adjustors
Prostate cancer (continued)					
DHA (continued)					
Netherlands Cohort Study Schuurman, 1999	1	0.01 g/d	1	1	Age, family history of prostate carcinoma, socioeconomic status, total energy intake, total energy-adjusted fat intake.
	2	0.03 g/d	0.82 (0.60, 1.13)	0.81 (0.58, 1.11)	
	3	0.06 g/d	1.01 (0.74, 1.38)	1.00 (0.73, 1.38)	
	4	0.09 g/d	1.07 (0.79, 1.46)	1.09 (0.80, 1.49)	
	5	0.18 g/d	1.05 (0.77, 1.42)	1.03 (0.75, 1.40)	
	Total n = 58,279		p = 0.19‡	p = 0.19‡	
Skin (BCC) cancer					
OMEGA-3					
Health Professionals Follow-up Study VanDam, 2000	1	0.07 g/d	1	1	Age, 2-year follow-up period, major ancestry, energy intake, BMI, hair color, frequency of routine physical examinations, cigarette smoking, mean annual solar radiation in region of residence, fat.
	2	0.15 g/d	0.98 NR	0.97 (0.86, 1.09)	
	3	0.24 g/d	1.07 NR	1.04 (0.93, 1.17)	
	4	0.34 g/d	1.07 NR	1.05 (0.93, 1.18)	
	5	0.58 g/d	1.14 NR	1.13 (1.01, 1.27)	
	Total n = 43,217		p = 0.003‡	p = 0.008‡	

Updated evidence table for prospective cohort studies of risk of different types of cancer for different categories of consumption of omega-3 FA, by category for each type of cancer. (updated October 2005)

Cohort Author, Year	Study arm (quartile, quintile or dose group)	Median intake	Estimates of effect		
			Age adjusted RR (95% CI)	Multivariate RR (95% CI)	Multivariate Adjustors
Stomach cancer					
FISH					
Fukuoka Prefecture Cohort, Japan Ngoan, 2002 [28] Stomach cancer *including* first 3 years follow-up	1	Low	NR	1	Age, sex, smoking, processed meat, liver, cooking or salad oil, suimono and pickled food.
	2	Medium	NR	1.1 (0.5, 2.3)	
	3	High	NR	1.0 (0.4, 2.2)	
	Total n = 13,000			p = 0.05‡	
Fukuoka Prefecture Cohort, Japan Ngoan, 2002 [28] Stomach cancer *excluding* first 3 years follow-up	1	Low	NR	1	
	2	Medium	NR	0.9 (0.4, 2.2)	
	3	High	NR	0.9 (0.3, 2.1)	
	Total n = 13,000			p = 0.05‡	

* NR = Not Reported; ‡ = test for trend.

References

INCLUDED STUDIES

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(See pages 127-194 of evidence report for complete listing of studies excluded prior to update)

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