Effects of Omega-3 Fatty Acids on Cancer Risk

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REVIEW

Effects of Omega-3 Fatty Acids on Cancer Risk

A Systematic Review

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Context Omega-3 fatty acids are purported to reduce the risk of cancer. Studies have reported mixed results.

Objective To synthesize published and unpublished evidence to determine estimates of the effect of omega-3 fatty acids on cancer risk in prospective cohort studies.

Data Sources Articles published from 1966 to October 2005 identified through MEDLINE, PREMEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, and CAB Health; unpublished literature sought through letters to experts in the neutraceutical industry.

Study Selection A total of 38 articles with a description of effects of consumption of omega-3 fatty acids on tumor incidence, prospective cohort study design, human study population; and description of effect of omega-3 among groups with different levels of exposure in the cohort were included. Two reviewers independently reviewed articles using structured abstraction forms; disagreements were resolved by consensus.

Data Extraction Two reviewers independently abstracted detailed data about the incidence of cancer, the type of cancer, the number and characteristics of the patients, details on the exposure to omega-3 fatty acids, and the elapsed time between the intervention and outcome measurements. Data about the methodological quality of the study were also abstracted.

Data Synthesis Across 20 cohorts from 7 countries for 11 different types of cancer and using up to 6 different ways to categorize omega-3 fatty acid consumption, 65 estimates of the association between omega-3 fatty acid consumption were reported. Among these, only 8 were statistically significant. The high degree of heterogeneity across these studies precluded pooling of data. For breast cancer 1 significant estimate was for increased risk (incidence risk ratio [IRR], 1.47; 95% confidence interval [CI], 1.10-1.98) and 3 were for decreased risk (RR, 0.68-0.72); 7 other estimates did not show a significant association. For colorectal cancer, there was 1 estimate of decreased risk (RR, 0.49; 95% CI, 0.27-0.89) and 17 estimates without association. For lung cancer one of the significant associations was for increased cancer risk (IRR, 3.0; 95% CI, 1.2-7.3), the other was for decreased risk (RR, 0.32; 95% CI, 0.13-0.76), and 4 other estimates were not significant. For prostate cancer, there was 1 estimate of decreased risk (RR, 0.43; 95% CI, 0.22-0.83) and 1 of increased risk (RR, 1.98; 95% CI, 1.34-2.93) for advanced prostate cancer; 15 other estimates did not show a significant association. The study that assessed skin cancer found an increased risk (RR, 1.13; 95% CI, 1.01-1.27). No significant associations between omega-3 fatty acid consumption and cancer incidence were found for aerodigestive cancer, bladder cancer, lymphoma, ovarian cancer, pancreatic cancer, or stomach cancer.

Conclusions A large body of literature spanning numerous cohorts from many countries and with different demographic characteristics does not provide evidence to suggest a significant association between omega-3 fatty acids and cancer incidence. Dietary supplementation with omega-3 fatty acids is unlikely to prevent cancer.

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STUDIES SHOW THAT TISSUE LEVels of arachadonic acid– and eicosopentaenoic acid (EPA)–derived eicosanoids influence many physiological processes, including calcium transport across cell membranes, angiogenesis, apoptosis, cell proliferation, and immune cell function.[1-4] These processes are integral to the immune system and hence the pathogenesis of autoimmune diseases 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 fatty acids may experience a lower prevalence of some types of cancer,[5-8] and many small trials have attempted to assess the effects of omega-3 fatty acids on cancer treatment by adding omega-3 fatty acid to the diet either as omega-3 fatty acid–rich foods or as dietary supplements.[9-22] In addition, dietary omega-3 fatty acids have been found to modulate mammary tumor formation and proliferation in rodents.[23]

In response to this evidence, a number of omega-3 fatty acid–containing dietary supplements have appeared on the market claiming to protect against the development of a variety of conditions including cancer. To assess the va-

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lidity of claims that omega-3 fatty acids prevent cancer, we systematically reviewed the literature for studies that evaluated the effect of omega-3 fatty acids on the incidence of cancer.

METHODS

The study on which this report is based is part of a larger systematic review of the medical literature regarding the effects of omega-3 fatty acid supplementation on both cancer incidence and cancer treatment in humans. Consequently, our initial search was broad. This report deals only with cancer incidence.

Identification of the Literature

We used electronic databases to identify published human studies about omega-3 fatty acids and cancer (complete search terms can be viewed in Appendix A.4 at http://www.ahrq.gov/downloads/pub/evidence/pdf/03cancer/03cancer.pdf). We did not restrict by language. The following databases were searched: MEDLINE (1966 through the fifth week of October 2003), PREMEDLINE (Nov 7, 2003), EMBASE (1980 through the 44th week of 2003), Cochrane Central Register of Controlled Trials (third quarter of 2003), CAB Health (1973 through October 2003. All of these databases were searched using the Ovid interface, except for CAB Health, which was searched through SilverPlatter. We subsequently updated our search in October 2005 using the same search strategy but restricting to observational study designs. The reference lists of studies that met our inclusion criteria were also searched for potentially relevant titles. External peer reviewers of a draft of this report were also asked to identify additional relevant studies that were not included in the draft. We also sent letters to industry experts recommended by the US Office of Dietary Supplements to obtain any unpublished data.

Evaluation of the Literature

Two of 4 reviewers (W.A.M., P.K., A.M.I., and Y.-W.L.) independently evaluated the citations and abstracts. The reviewers flagged article titles that focused on omega-3 fatty acids and cancer. Articles that either reviewer flagged were ordered, as were articles from whose abstracts and titles relevance could not be determined. Two of the 4 reviewers independently reviewed each article that was obtained to determine whether it met inclusion criteria using a structured screening form. The reviewers resolved any disagreements by consensus. Inclusion criteria included description of effects of consumption of omega-3 fatty acids on tumor incidence, prospective cohort study design, human study population, and description of effects of exposure to omega-3 with different levels of exposure in the cohort. Although parameters of methodological quality were evaluated, they were not used as inclusion criteria. Language was not a barrier to inclusion. We excluded case-control studies because they are highly susceptible to methodological biases, especially recall bias.

All stages of the review were performed independently by reviewers trained in health services research and the principles of critical appraisal; at least 1 reviewer was a physician. The reviewers resolved differences through consensus, and a senior physician researcher (C.H.M.) resolved any disagreements.

Data Extraction

For the articles that passed our screening criteria, 2 reviewers independently abstracted detailed data about the incidence of cancer, the type of cancer, the number and characteristics of the patients, details on the exposure to omega-3 fatty acids, and the elapsed time between the intervention and outcome measurements. 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, adjustment for confounders, and blinded assessment of exposure and case status when ascertaining case and exposure status, respectively.[24,25] A score for quality was not calculated for observational studies, for there is no validated method to do so.[26]

Data Synthesis

For this report, we constructed a detailed summary table, stratified by cancer type, which describes the multivariate-adjusted risk ratios (RRs) that were reported for the study group with the highest intake of omega-3 fatty acid relative to the study group with the lowest intake. This table details the specific categories of omega-3 consumption for which the RRs were reported, ie, total omega-3, marine omega-3, linolenic acid (ALA), EPA, or docosahexaneoic acid (DHA) and fish, which can reasonably be used as a surrogate for omega-3 consumption given the high omega-3 content of fish. We describe the median intake of the relevant omega-3 fatty acid for the study groups, 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 participants 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, and 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.

Given the marked heterogeneity of the identified studies in terms of omega-3 fatty acid components reported, amount of omega-3 fatty acid consumed and exposure time to omega-3 fatty acids, it was not reasonable to pool data across studies. To evaluate the possible effect of sample size on the reported estimates of risk, we produced plots of the RRs on which the point estimate for each risk estimate was sized according to the inverse of the variance for each risk estimate.

RESULTS

Literature Search

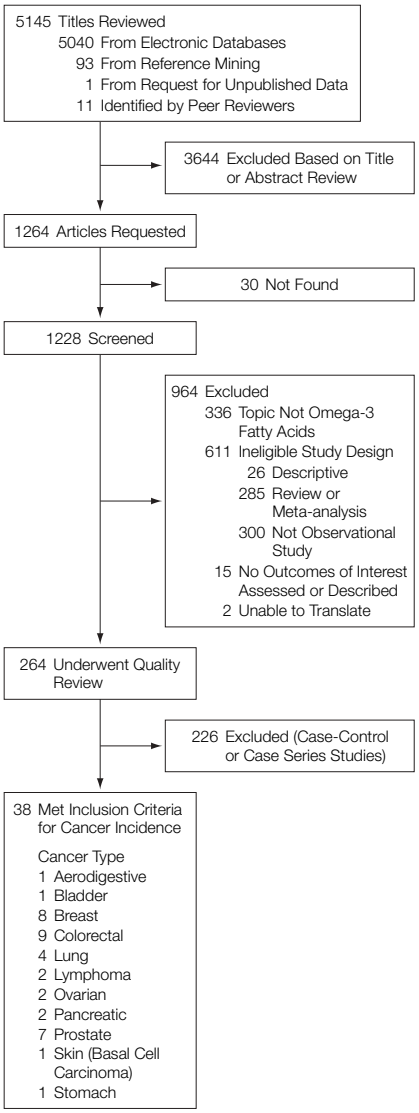
Results from our literature search are detailed in FIGURE 1. Our search identified 5040 citations from the electronic databases; 93 additional citations were identified through reference mining; a request for unpublished data yielded one citation; peer reviewers of a draft of this report identified 11 citations. In total we reviewed 5145 citations. Our reviewers considered 1264 of these article titles to be potentially relevant to our research topic. We were able to retrieve 1228 (97%) of these articles. Of the articles retrieved, 264 were accepted for further review because they reported on results from observational studies of omega-3 fatty acid in the treatment of cancer. Of the 264 articles that went to further review, a total of 226 were rejected because their study designs were either case-control or case series, which did not meet our inclusion criteria.

The remaining 38[5-8,27-60] reports described the effect of omega-3 fatty acid on the incidence of 11 different types of cancer among participants enrolled in 20 different prospective cohorts. The characteristics of the 20 cohorts in which cancer incidence was studied are summarized in TABLE 1. These cohorts ranged in size from 6000 to 121 000, with from 9000 to 1.5 million person-years of observation. Together, these cohorts include more than 700 000 participants and 3 million person-years of observation. The observation periods in these cohorts ranged from 3 to 30 years. 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 acid, fish or marine omega-3 fatty acid, or as the specific omega-3 fatty acid ALA, EPA, DHA, or all 3. 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 1 to 24 years after dietary information was obtained and was typically ascertained using population cancer registries.

The methodological quality of the studies was variable. All of the cohorts reported valid methods to ascertain exposure to omega-3 fatty acids and cancer incidence. Likewise, all of the cohorts reported adjustment for confounders, although the variables used in multivariable analyses varied among the studies. All but 2 of the cohorts provided descriptions of withdrawals and dropouts.[35,41] Blinded assessment of exposure and case status when ascertaining case and exposure status, respectively, was reported for only 3 cohorts: the Health Professionals Follow-up Study,[36,54,57-59] the Netherlands Health Study,[7,8] and the Nurses' Health Study.[30,31,38,48,49,52]

More than half of these reports described the effect of omega-3 fatty acid on 1 of 3 types of cancer: breast,[7,29-35] colorectal,[5,36-43] and prostate.[8,53-58] The remaining publications described the effects of omega-3 fatty acid on the incidence of 8 different types of cancer with only 1 or 2 publications describing the effects on each of the following types of cancer: aerodigestive, bladder, lung, lymphoma (non-Hodgkin), ovarian, pancreatic, skin (basal cell carcinoma), and stomach. The reported effects of omega-3 fatty acids on the incidence for each type of cancer are described below. The RRs for developing each of these types of cancer for the highest consumption group (quartile, quintile, dose group, etc) relative to the lowest consumption group for fish, total omega-3 fatty acid, marine omega-3 fatty acid, ALA, DHA, and EPA are detailed in FIGURE 2 and FIGURE 3 and in TABLE 2 and TABLE 3. A comprehensive evidence table that includes information about the study groups with intermediate levels of omega-3 fatty acid consumption can be viewed in Appendix D at http://www.ahrq.gov/downloads/pub/evidence/pdf/03cancer/03cancer.pdf.

Figure 1. Literature Flow to Assess the Effects of Omega-3 Fatty Acid on Tumor Incidence



Aerodigestive Cancer

We identified one study[27] 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 or pharynx, esophagus, or larynx among institutionalized US men of Japanese ancestry who resided on the Hawaiian island of Oahu. 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 RR of developing aerodigestive tract cancer was 1.37 (95% confidence interval [CI], 0.70-2.69) for men consuming fish 5 times per week or more.

Table 1. Characteristics of Cohorts That Have Described the Effects of Omega-3 Fatty Acid on Cancer Incidence

Source	No. of Participants in Cohort*	Base Population	Birth Years of Participants	Observation Period		Method of Cancer Ascertainment
				Omega-3 Exposure	Cancer Incidence	
			Upper Aerodigestive			
Honolulu Heart[27]	8006	Institutionalized US men of Japanese ancestry residing on Oahu	1900-1919	1965-1968†	1965-1993	Oahu hospitalizations for cancer and Hawaii Tumor Registry‡
			Bladder			
Honolulu Heart[28]	8006	Institutionalized US men of Japanese ancestry residing on Oahu	1900-1919	1965-1968§	1965-1993	Oahu hospitalizations for cancer and Hawaii Tumor Registry
			Breast			
Diet, Cancer, and Health Study[29]	29 875	Population of greater Copenhagen and Aarhus, Denmark	1929-1947	1993-1997§	1993-2000	Cancer registry
Life Span Study[33]	≅120 000	Survivors of atomic bomb in Hiroshima or Nagasaki, Japan, who were alive on September 1, 1969	Not described	1969-1970, 1979	1969-1993, 1981-1983	Hiroshima and Nagasaki cancer registries
The Netherlands[7]	62 573	Population of the Netherlands	1917-1931	1986	1986-1992	Regional cancer registries
Norwegian[34]	14 729	Population of Norway	1925-1942	1974-1977	11-14 y follow-up mean = 12	National Cancer Registry
Singapore Chinese Health Study[35]	63 257	Permanent residents or citizens of Singapore living in government housing estates speaking Hokkien or Cantonese	1919-1953	1993-1998	Enrollment -2000	Singapore Cancer registry
Nurses' Health Study[30-32]	121 700	US female registered nurses	1921-1946	1980, 1984, 1986, 1990, 1994	1980-1994	Self-report or vital records confirmed by medical records review
			Colorectal			
Health Professionals[36]	51 529	US male dentists, optometrists, osteopathic physicians, physicians, podiatrists, pharmacists, and veterinarians who responded to a postal questionnaire	1911-1946	1986, 1990, 1994	1986-1998	Self-report or vital records confirmed by medical records review
Iowa Women's Health[40]	41 837	Women with valid Iowa driver's license	1917-1931	1986	1986-1992	State Health Registry of Iowa
The Netherlands[37]	62 573	Population of the Netherlands	1917-1931	1986	1986-1992	Regional cancer registries
NY University Women's Health[5]	14 727	Women treated at the Guttman Breast Diagnostic Institute in New York City or at the Strax Breast Cancer Institute in Florida	1920-1957	1985-1991	1985-1992	Self-report confirmed by medical records review supplemented by review of state cancer registries and National Death Index
Nurses' Health Study[38]	121 700	US female registered nurses	1921-1946	1980, 1984, 1986, 1990, 1994	1980-1994	Self-report or vital records confirmed by medical records review
Swedish Women[39,42]	61 463	Participants of population-based mammography screening program in Sweden	1925-1939	1987-1990, 1997	Enrollment-1998	Regional cancer registries
Women's Health Study[41]	37 547	US female health professionals enrolled in randomized controlled trial of aspirin, vitamin E and placebo	1917-1945	1992-1995	1993-2003	Self-report confirmed by medical records reviewed by state cancer registries and National Death Index

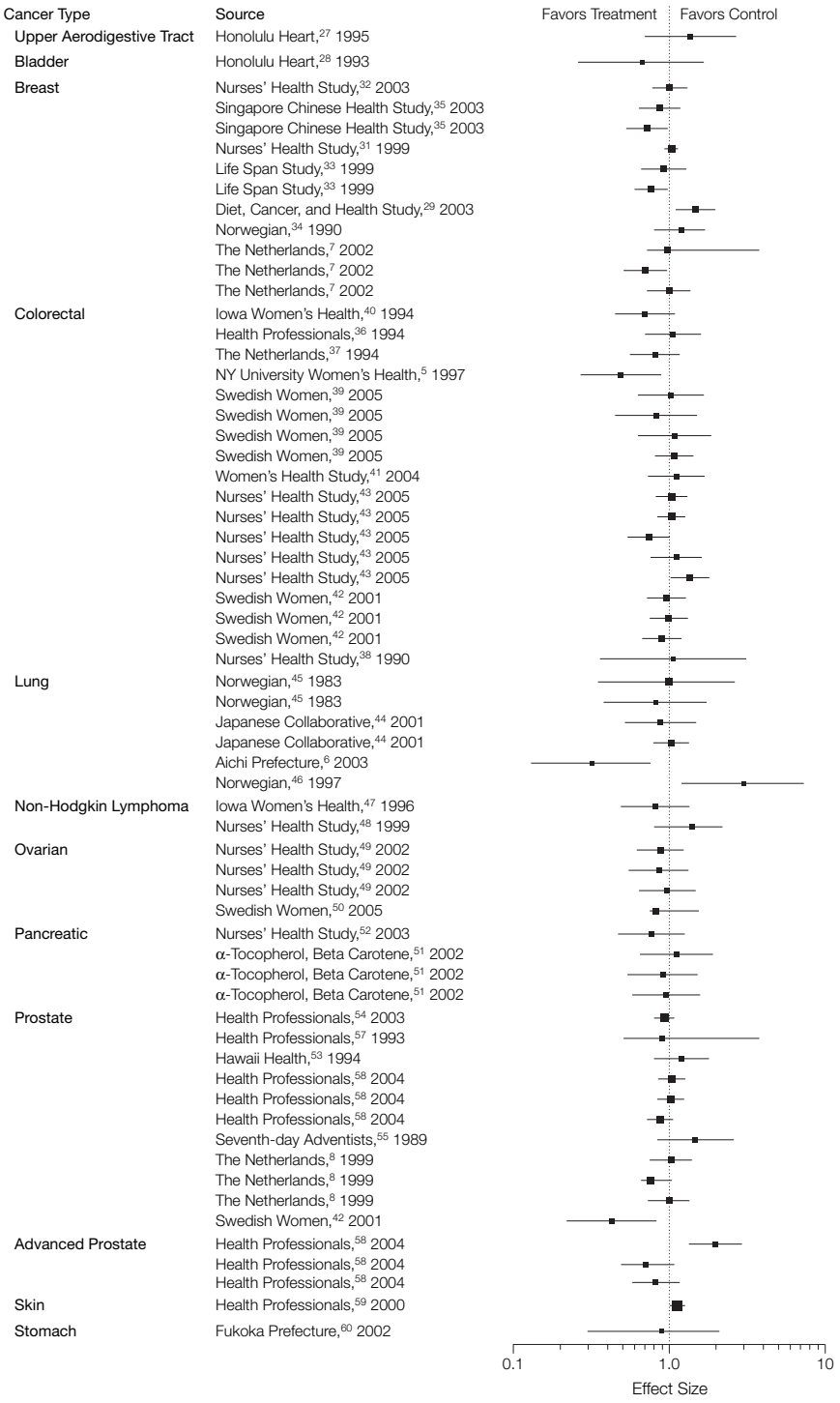
(continued)

Table 1. Characteristics of Cohorts That Have Described the Effects of Omega-3 Fatty Acid on Cancer Incidence (cont)

Source	No. of Participants in Cohort*	Base Population	Birth Years of Participants	Observation Period		Method of Cancer Ascertainment
				Omega-3 Exposure	Cancer Incidence	
Lung						
Aichi Prefecture[6]	9753	Population of Aichi Prefecture, Japan	1917-1972	1986-1989†	1985-1999	Self-report or death certificate
Japanese Collaborative[44]	110 792	Population of 19 prefectures in Japan	1909-1950	1988-1990	1988-1997	Death certificates
Norwegian[45]	16 713	Population of Norway	Not reported	One-time questionnaire between 1967 and 1969	From questionnaire until 1978	Cancer registry
Norwegian[46]	14 729	Population of Norway	1925-1942	1974-1977	11-14 y follow-up, mean = 12	National Cancer Registry
Non-Hodgkin Lymphoma						
Iowa Women's Health Study[47]	41 837	Women with valid Iowa driver's license	1917-1931	1986	1986-1992	State Health Registry of Iowa
Nurses' Health Study[48]	121 700	US female registered nurses	1921-1946	1980, 1984, 1986, 1990, 1994	1980-1994	Self-report or vital records confirmed by medical records review
Ovarian						
Nurses' Health Study[49]	121 700	US female registered nurses	1921-1946	1980, 1984, 1986, 1990, 1994	1980-1994	Self-report or vital records confirmed by medical records review
Swedish women[53]	61 463	Participants of population-based mammography screening program in Sweden	1925-1939	1987-1990, 1997	Enrollment-1998	Regional cancer registries
Pancreatic						
Alpha-tocopherol, Beta-Carotene[51]	27 111	Male smokers in southwestern Finland enrolled in RCT of treatment with α-tocopherol or beta carotene	1916-1938	1985-1988†	1985-1997	Tumor registry with medical records verification
Nurses' Health Study[52]	121 700	US female registered nurses	1921-1946	1980, 1984, 1986, 1990, 1994	1980-1994	Self-report or vital records confirmed by medical records review
Prostate						
Hawaii Health[53]	8881	Male Hawaiians of Japanese, European, Filipino, Hawaiian, or Chinese ancestry	Not described	1975-1980	1975-1989	Hawaii tumor registry
Health Professionals[54,57,58]	51 529	US male dentists, optometrists, osteopathic physicians, podiatrists, pharmacists, and veterinarians who responded to a postal questionnaire	1911-1946	1986, 1990, 1994	1986-1998	Self-report or vital records confirmed by medical records review
The Netherlands[8]	62 573	Population of the Netherlands	1917-1931	1986	1986-1992	Regional cancer registries
Seventh-day Adventists[55]	Not described	Seventh-day Adventist households in California	Not described	1976	1976-1982	Self-report confirmed by medical records review and cancer registry
Swedish Twin Registry[56]	6272	Male twin pairs residing in Sweden in 1961	1886-1925	1967	1967-1997	National cancer and death registries
Skin, Basal Cell Carcinoma						
Health Professionals[59]	51 529	US male dentists, optometrists, osteopathic physicians, podiatrists, pharmacists, and veterinarians who responded to a postal questionnaire	1911-1946	1986, 1990, 1994	1986-1998	Self-report or vital records confirmed by medical records review
Stomach						
Fukuoka Prefecture[60]	13 250	Population of Fukuoka Prefecture, Japan	1880-1974	1986-1989†	Not stated	Not explicitly stated; infer death certificates from text

*Total number of participants enrolled in cohort. The number may differ from number of participants in analyses of specific diseases.
†Ascertained from single questionnaire at enrollment during described time frame.

Figure 2. Risk of Developing Cancer for Participants in the Highest Grouping vs Those in the Lowest Grouping of Omega-3 Fatty Acid Intake by Cancer Type



Because variance and sample size are approximately inversely related, the point estimates for studies with larger sample sizes are represented with larger boxes and the point estimates for studies with smaller sample sizes are represented with smaller boxes on the plots.

Bladder Cancer

We identified one study[28] that evaluated the effect of fish consumption on the incidence of urinary bladder cancer among institutionalized US men of Japanese ancestry who resided on the Hawaiian island of Oahu. 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 RR of developing bladder cancer was 0.67 (95% CI, 0.26-1.67) for men consuming fish 5 times per week or more.

Breast Cancer

We identified 8 studies[7,29-35] from 6 different cohorts that evaluated the effect of omega-3 fatty acid on the incidence of breast cancer. Breast cancer incidence relative to fish consumption was reported in 4 studies,[29,30,33,34] incidence relative to total[32,35] and marine omega-3 fatty acid[35] consumption was reported in 2, and incidence relative to each of the specific omega-3 fatty acid, DHA, EPA, and ALA was reported in 1 study.[7] Among the 4 studies that assessed the relationship between fish intake and breast cancer, 1 demonstrated an increased risk for women in the highest quartile of fish intake relative to women in the lowest quartile (incidence RR [IRR], 1.47; 95% CI, 1.10-1.98),[29] 1 demonstrated a reduced risk among women with "unknown" dried fish intake relative to women who consumed 1 or fewer servings per week (RR, 0.77; 95% CI, 0.60-0.98) but no association with "not dry" fish[33] and 2 found no association between fish consumption and the risk of breast cancer. Neither of the 2 studies that assessed the effect of total omega-3 fatty acid consumption on breast cancer risk reported an association with breast cancer. However, 1 of these studies[35] found a reduced risk for women in the highest quartile of marine omega-3 fatty acid consumption relative to those in the lowest quartile of consumption (RR, 0.72; 95% CI, 0.53-0.98). The one study[7] that assessed the effects of ALA, EPA, and DHA consumption on breast cancer risk reported a reduced risk for

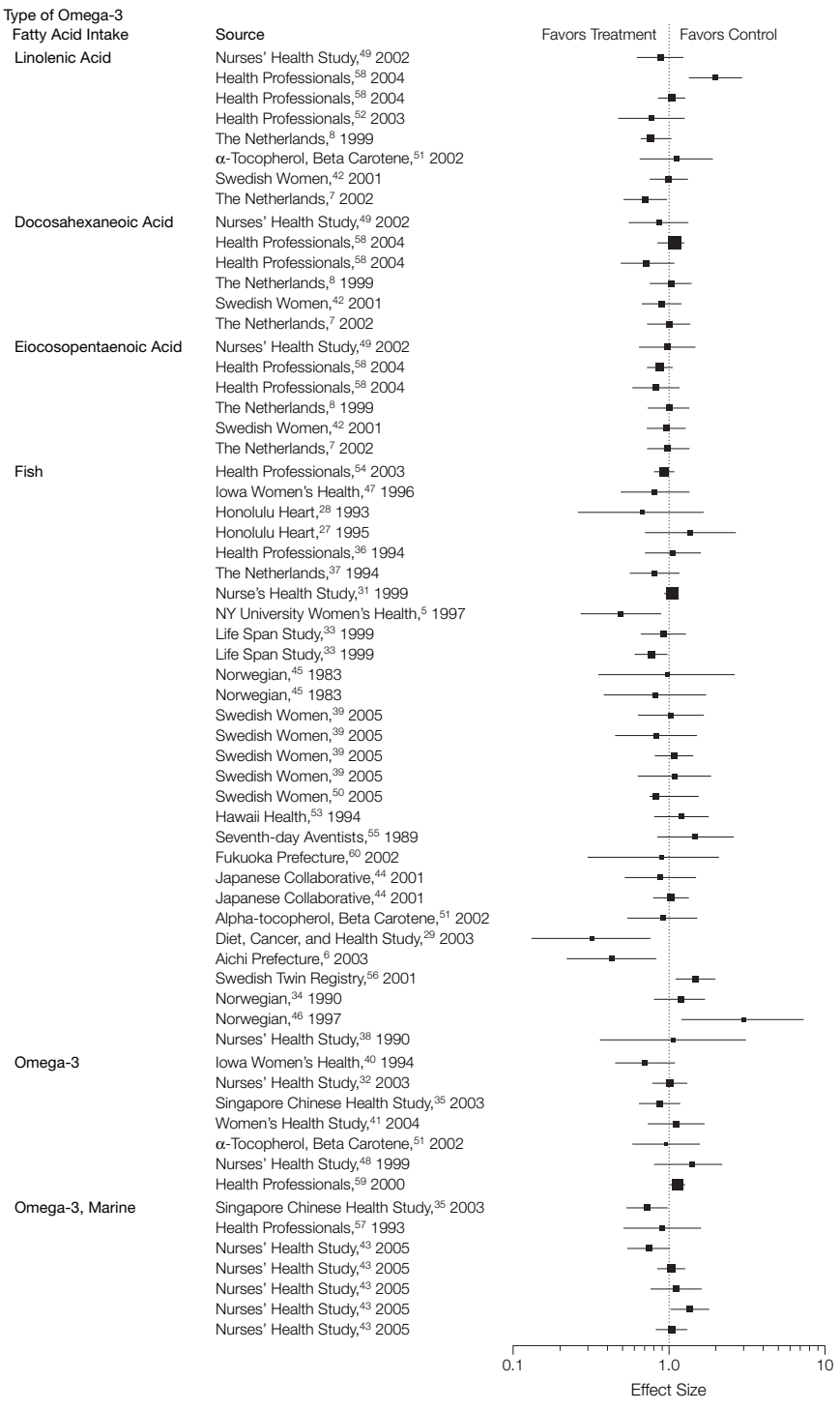
women in the highest vs lowest quintiles of ALA consumption (RR, 0.70; 95% CI, 0.51-0.97); associations between ALA consumption and breast cancer incidence were not significant for comparisons between the other quintiles and the lowest quintiles. There was no association between incidence of breast cancer and consumption of either EPA or DHA.

Among these cohorts, 2 assessed the effect of menopausal status on the association between omega-3 fatty acids and cancer incidence. In stratified analyses, the Nurses' Health Study, which found no association between either fish consumption or total omega-3 consumption among all women, also found no association between fish intake and the incidence of breast cancer among premenopausal or postmenopausal women.[30] In this same cohort, marine omega-3 fatty acid consumption was associated with a small increased risk of breast cancer among postmenopausal women (RR, 1.09; 95% CI, 1.02-1.17), but not for premenopausal women.[31] The Singapore Chinese Health Study reported that the reduced incidence of breast cancer associated with marine omega-3 fatty acid consumption was confined to postmenopausal women and to women with advanced stage disease (stage II or greater).[35]

The relationship between fish intake, estrogen receptor positivity, and cancer incidence was assessed in 1 study.[29] In this study, the incidence RR for breast cancer per mean intake of 25 g/d of fish was 1.14 (95% CI, 1.03-1.26) for estrogen receptor–positive women and 1.00 (95% CI, 0.81-1.24) for estrogen receptor–negative women.

The relationship between breast cancer incidence, marine omega-3 fatty acid intake, and omega-6 fatty acid intake was examined in 1 study.[35] In this study, among participants in the lowest quartile of marine omega-3 fatty acid consumption, breast cancer risk increased significantly with increasing levels of omega-6 fatty acid consumption (*P* for trend=.08). Relative to women in the lowest quartile of both

Figure 3. Risk of Developing Cancer for Participants in the Highest Grouping vs Those in the Lowest Grouping of Omega-3 Fatty Acid Intake by Omega-3 Fatty Acid Type



Because variance and sample size are approximately inversely related, the point estimates for studies with larger sample sizes are represented with larger boxes and the point estimates for studies with smaller sample sizes are represented with smaller boxes on the plots.

omega-6 and marine omega-3 consumption, the RR 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).

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 in 1 study.[30] In another study, occupational status and body mass index, calculated as weight in kilograms divided by the square of height in meters, did not affect the reported association between fish consumption and breast cancer incidence.[34]

Colorectal Cancer

We identified 9 studies[5,36-43] from 7 different cohorts that evaluated the effect of omega-3 fatty acid on the incidence of colorectal cancer. Colorectal cancer incidence relative to fish consumption was reported in 5 studies[5,36-39]; incidence relative to total omega-3 fatty acid consumption in 2[40,41]; relative to marine

Table 2. Risk of of Cancer From Omega-3 Fatty Acid Intake by Aerodigestive Tract, Bladder, Breast, and Colorectal Cancer

Study	No. of Participants in Analyses	Median Intake		Multivariate Adjusted Risk Ratio (95% CI)					
		Referent Group	Highest Intake Group	Fish	Total Omega-3	Marine Omega-3	ALA	EPA	DHA
Upper Aerodigestive Tract									
Honolulu Heart[27]	7995	<1 g/wk	≥5 g/wk	1.37 (0.70-2.69)[a]					
Bladder									
Honolulu Heart[28]	7995	<1 g/wk	≥5 g/wk	0.67 (0.26-1.67)[a]					
Breast									
Diet, Cancer, and Health Study[29]	23 693	0-26 g/d	>58 g/d	1.47 (1.10-1.98)					
Life Span Study[33]	34 759	≤1 Times/wk	Unknown	0.92 (0.66-1.29)[a,b,c]					
The Netherlands[7]	62 573	0.6 g/d ALA 0 g/d EPA 0.01 g/d DHA	1.7 g/d ALA 0.08 g/d EPA 0.14 g/d DHA				0.70 (0.51-0.97)[f]	0.98 (0.72-1.35)	1.00 (0.72-1.37)
Norwegian[34]	14 500	≤2 g/wk	≥2 g/wk	1.2 (0.8-1.7)[a,d]					
Nurses Health Study[30]	88 647	≤0.13 Servings/d	≥0.4 Servings/d	1.04 (0.93-1.14)[a]					
Nurses' Health Study[32]	88 410	0.03% Of energy intake	0.19% Of energy intake		1.01 (0.78-1.31)[a]				
Singapore Chinese Health Study[35]	35 298	Not reported	Not reported		0.87 (0.64, 1.18)[a]	0.72 (0.53-0.98)[a]			
Colorectal									
Health Professionals[36]	47 949	8.4 g/d	83.4 g/d	1.06 (0.70-1.60)[a,e]					
Iowa Women's Health Study[40]	35 215	<0.03 g/d	>0.18 g/d		0.70 (0.45-1.09)[a]				
The Netherlands[37]	3111	0 g/d	>20 g/d	0.81 (0.56-1.17)[a]					
NY University Women's Health Study[5]	14 727	Not reported	Not reported	0.49 (0.27-0.89)[f]					
Nurses' Health Study[38]	88 751	<1 g/mo	4 g/wk	1.06 (0.36-3.12)[a]					
Nurses' Health Study,[43] 2005	34 451	0.03% Of energy	0.18% Of energy			1.04 (0.84-1.27)[a,r] 0.74 (0.54-1.01)[a,s] 1.36 (1.02-1.81)[a,t] 1.04 (0.82-1.32)[a,u] 1.11 (0.76-1.62)[a,j]			
Swedish women[39]	61 433	0.5 servings of fish/wk	≥2 servings of fish/wk	1.08 (0.81-1.43)[a,g] 1.03 (0.63-1.67)[a,h] 0.83 (0.45-1.51)[a,i] 1.08 (0.63-1.86)[a,j]					
Swedish women[42]	61 433	0.03 g EPA/d 0.08 g DHA/d	0.09 g EPA/d 0.18 g DHA/d				0.99 (0.75-1.32)[a,i] 1.11 (0.70-1.78)[a,j] 0.90 (0.63-1.28)[a,k]	0.85 (0.60-1.21)[a,k] 1.25 (0.75-2.06)[a,j] 0.96 (0.72-1.28)[a,i]	0.90 (0.67-1.20)[a,i] 1.03 (0.62-1.71)[a,j] 0.88 (0.61-1.26)[a,k]
Women's Health Study[41]	37 547	Not reported	Not reported		1.11 (0.73-1.69)[a]				

Abbreviations: ALA, linolenic acid; CI, confidence interval; DHA, docosahexaneoic acid; EPA, eicosopentaenoic acid.
[a]Test for trend across all consumption groups insignificant.
[b]For "fish not dry."
[c]Point estimate, for dry fish 0.77 (95% CI, 0.60-0.98), *P* for trend is .03.
[d]Incidence rate ratio.
[e]Adjusted for age only.
[f]*P* for trend ≤.05.
[g]Cancer of proximal colon.
[h]Cancer of distal colon.
[i]Colorectal cancer.
[j]Cancer of rectum.
[k]Cancer of colon.
[l]Men.
[m]Women.
[n]Histologic verification.
[o]Squamous and non-small cell.
[p]95% CI not reported but estimated from data presented in manuscript.
[q]Advanced prostate cancer.
[r]Adenoma.
[s]Cancer of large bowel.
[t]Cancer of small bowel.
[u]Cancer of distal colon.

omega-3 fatty acids in one study (this was 62 there is none in the list); and relative to each of the specific omega-3 fatty acid, DHA, EPA, and ALA in one.[42]

Among the studies that measured fish consumption, 4 found no association with the incidence of colorectal cancer[36-39]; 1 study[5] demonstrated a reduced risk among participants in the highest quartile of fish intake relative to participants in the lowest quartile of fish intake (RR, 0.49; 95% CI, 0.27-0.89).

Table 3. Risk of of Cancer From Omega-3 Fatty Acid Intake by Lung, Non-Hodgkin Lymphoma, Ovarian, Pancreatic, Prostate, Skin, and Stomach Cancer*

Study	No. of Participants in Analyses	Median Intake		Multivariate Adjusted Risk Ratio (95% CI)					
		Referent Group	Highest Intake Group	Fish	Total Omega-3	Marine Omega-3	ALA	EPA	DHA
Lung									
Aichi Prefecture[6]	5885	<1 Time/wk	≥3 Times/wk	0.32 (0.13-0.76)[f]					
Japanese Collaborative[44]	98 248	≤1-2 Times/wk	Almost every day	1.03 (0.79-1.34)[a,l] 0.88 (0.52-1.49)[a,m]					
Norwegian[45]	13 785	<10 Times/mo	≥20 Times/mo	0.82 (0.38-1.74)[a,n,p] 0.98 (0.35-2.64)[a,o,p]					
Norwegian[46]	51 452	<1 Times/wk	≥5 Time/wk	3.0 (1.2-7.3)[a,d]					
Non-Hodgkin Lymphoma									
Iowa Women's Health Study[47]	35 156	<4 Servings/mo	>6 Servings/mo	0.81 (0.49-1.35)[a]					
Nurses' Health Study[48]	88 410	0.02% Of energy intake	0.10% Of energy intake		1.4 (0.8-2.2)				
Ovarian Cancer									
Nurses' Health Study[49]	80 258	Not reported	Not reported				1.00 (0.72-1.39)[a]	0.97 (0.64-1.48)[a]	1.07 (0.71-1.63)[a]
Swedish Women[50]	61 057	<1 Servings/wk	≥3 Servings/wk	0.82 (0.75-1.55)[a]					
Pancreatic Cancer									
α-Tocopherol, Beta-Carotene Cancer Prevention Study[51]	27 111	Not reported	Not reported	0.91 (0.54-1.52)[a]	0.96 (0.58-1.58)[a]		1.11 (0.65-1.91)[a]		
Nurses' Health Study[52]	88 802	0.7 g/d	1.1 g/d				0.77 (0.47-1.26)[a]		
Prostate Cancer									
Hawaii Health[53]	8881	Not reported	Not reported	1.2 (0.8-1.8)[a]					
Health Professionals[54]	47 882	<2 Times/mo	>3 Times/wk	0.93 (0.80-1.08)					
Health Professionals[57]	47 855	0.05 g/d	0.55 g/d		0.90 (0.51-1.61)[a]				
Health Professionals[58c]	47 866	<0.37% Of energy for ALA <0.014% Of energy for EPA <0.032% Of energy for DHA	>0.58% Of energy for ALA >0.066% Of energy for EPA >0.066% Of energy for DHA				1.04 (0.85-1.27)[a] 1.98 (1.34-2.93)[f,q]	0.87 (0.72-1.06)[f] 0.82 (0.58-1.17)[a,q]	1.02 (0.84-1.25) 0.71 (0.49-1.08)[a,q]
The Netherlands[8]	58 279	0.7 g/d ALA 0 g/d EPA 0.01 g/d DHA	2.1 g/d ALA 0.10 g/d EPA 0.18 g/d DHA				0.76 (0.66-1.04)[a]	1.0 (0.73-1.35)[a]	1.03 (0.75-1.40)[a]
Seventh-day Adventists[55]	14 000	Never	≥1 g/wk	1.47 (0.84-2.60)[f]					
Swedish Twin Registry[56]	6272	Never/seldom	Large	1.0 (0.7-1.6)[f]					
Skin, Non–Basal Cell Carcinoma									
Health Professionals[59]	43 217	0.07 g/d	0.58 g/d		1.13 (1.01-1.27)[f]				
Stomach									
Fukuoka Prefecture[60]	13 000	Low	High	1.0 (0.4-2.2)[f]					

Abbreviations: ALA, linolenic acid; CI, confidence interval; DHA, docosahexaneoic acid; EPA, eicosopentaenoic acid.
*For footnote designations, see Table 2.

Among the 2 studies that measured total omega-3 fatty acid consumption, 1 demonstrated a trend for reducing the risk of colorectal cancer with higher consumption of omega-3 fatty acid when adjusting only for age[40]; the other did not find an association.[41] However, with adjustment for multiple variables no significant association was observed between omega-3 fatty acid consumption and the incidence of colorectal cancer. Likewise, the study that measured marine omega-3 fatty acid consumption demonstrated a trend for reducing the risk of cancer of the large bowel with higher consumption of marine omega-3 fatty acid when adjusting only for age but not with adjustment for multiple variables. This same study found no association between marine omega-3 fatty acids and adenomas or with cancers of the small bowel, distal colon, or rectum. No significant association with the incidence of colorectal cancer was found with ALA, DHA, or EPA consumption.[42]

Five of the studies[5,38-41] involved 3 different cohorts of women, 1 involved a cohort of men,[36] and 2 included cohorts of men and women.[37,42] Among the latter, 1 study performed subgroup analyses among men and women and found no association between fish consumption and colon cancer for men or women.[37] The study that demonstrated a favorable association between a source of omega-3 fatty acid and incidence of colorectal cancer after adjustment for multiple variables was performed in a cohort of women.[5]

Three of the studies assessed the incidence of colon cancer only[37,38,40] and 6 assessed the incidence of colorectal cancer including cancers of the colon or rectum.[5,36,39,41-43] In 2 studies from the same cohort that assessed the incidence of colon cancer, rectal cancer, and colorectal cancer,[39,42] no difference was found in the association between fish, ALA, EPA, or DHA intake and the incidence of any of these types of cancer, ie, there was no association in any case. The study that demonstrated a favorable association between a source of omega-3 fatty acid and incidence of colorectal cancer after adjustment for multiple variables included both cancers of the colon and rectum to define colorectal cancer.[5]

Lung Cancer

We identified 3 studies[6,45,46] from 3 different cohorts that evaluated the effect of omega-3 fatty acid on the incidence of lung cancer and 1 that evaluated the effect of omega-3 fatty acid intake on death from lung cancer.[44] All of these studies assessed lung cancer incidence relative to fish consumption. In 1 study,[6] fish consumption was associated with a reduced risk of lung cancer (RR, 0.32; 95% CI, 0.13-0.76). In another study, fish consumption was associated with an increased risk of lung cancer[46] (IRR, 3.0; 95% CI, 1.2-7.3). In the other studies, no significant association was found between fish intake and lung cancer incidence[45,46] or death from lung cancer.[44]

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 1 study,[6] 19 Japanese prefectures in another study,[44] and people residing in Norway in the other 2.[45,46] One study reported the risk of dying from lung cancer stratified by sex.[44] This study found no significant association between fish consumption and death from lung cancer for either men or women.

Lymphoma

We identified 2 studies from 2 different cohorts that evaluated the effect of omega-3 fatty acid on the incidence of non-Hodgkin lymphoma.[47,48] 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 lymphoma.

Both cohorts were restricted to women. The Nurses' Health Study cohort includes US women who are registered nurses who responded to a mailed questionnaire.[48] The Iowa Women's Health Study cohort includes women who had valid Iowa driver's licenses at the time of recruitment.

Ovarian

We identified 2 reports[49,50] that evaluated the effect of omega-3 fatty acids on the incidence of ovarian cancer. In 1 there was no association between fish consumption and the incidence of ovarian cancer.[50] The other found no effect of different kinds of fat, including the omega-3 fatty acids DHA, EPA, and ALA, on the incidence of ovarian cancer among women enrolled in the Nurses Health Study.[49] In this latter study, no evidence of an association between intake of any type of fat including DHA, EPA, and ALA and the incidence of ovarian cancer was found. Secondary analyses showed that total fat intake (ie, 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 fatty acids specifically.

The participants in the first study were women from a population-based sampling of several counties in Sweden. The participants in the latter study were all female registered nurses in the United States.

The latter study assessed for several different subpopulations the effect of total fat intake, but not omega-3 fat intake, on the development of ovarian cancer. The relation between fat intake and ovarian cancer risk (ie, no association) did not differ substantially by age or menopausal status. The effects of several covariates on the effect of total fat intake but not omega-3 fat were also 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.

Pancreatic Cancer

We identified 2 studies[51,52] from 2 different cohorts that evaluated the effect of omega-3 fatty acid on the incidence of pancreatic cancer. One study assessed incidence relative to fish,

omega-3 fatty acid, and ALA consumption[51]; the other assessed incidence relative to ALA consumption.[52] There was no significant association between fish intake and any of these measures of omega-3 fatty acid in either study.

One cohort comprised women, the other of men. In the Nurses Health Study, participants responded to a mailed questionnaire.[52] The Alpha-tocopherol, Beta-Carotene Cancer Prevention Study cohort includes men who smoke.

Prostate Cancer

We identified 7 studies[8,53-58] from 5 different cohorts that evaluated the effect of omega-3 fatty acid on the incidence of prostate cancer. Prostate cancer incidence relative to fish consumption was reported in 4 studies,[53-56] relative to marine omega-3 fatty acid consumption in 1,[57] relative to the specific omega-3 fatty acid DHA and EPA in 2,[8,58] and relative to the specific omega-3 fatty acid ALA in 3.[8,57,58] Among the 4 studies that assessed risk relative to fish consumption, 1 demonstrated a favorable effect (risk for never/seldom consumption relative to moderate consumption [RR, 2.3; 95% CI, 1.2, 4.5),[56] 1 showed a trend toward a favorable effect,[55] and 2 did not find an association.[53,54] For ALA, there was no association with overall prostate cancer risk in 2 studies,[8,58] However, 1 of these studies demonstrated increased risk for advanced prostate cancer (RR, 1.98; 95% CI, 1.34-2.93) for highest vs lowest quintile of ALA consumption).[58] No significant association with the incidence of prostate cancer was found with marine omega-3 fats,[57] EPA, or DHA consumption.[8,58]

All analyses were restricted to men of racial groups that were homogeneous within but that differed across the studies. These studies followed up cohorts that are ethnically, geographically, socioeconomically distinct. The base populations for these studies comprised Hawaiian men of Japanese ancestry,[53] Seventh-day Adventist men residing in California,[55] US male health care professionals,[54] Swedish male twin pairs,[56] and the Dutch population.[8]

Skin Cancer (Basal Cell Carcinoma)

One study[59] evaluated the effect of omega-3 fatty acid on the incidence of skin cancer among male health care professionals. This study assessed incidence of basal cell carcinoma relative to omega-3 fatty acid consumption. Relative to participants in the lowest quartile of omega-3 fat consumption, those 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).

Stomach Cancer

We identified 1 study[60] that evaluated the effect of omega-3 fatty acid on the incidence of stomach cancer. This study assessed incidence relative to fish consumption and found no association with the incidence of stomach cancer.

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

COMMENT

Among 65 estimates of association calculated across 20 different cohorts for 11 different types of cancer and 6 different ways to assess omega-3 fatty acid consumption, only 10 are statistically significant. Significant associations between omega-3 fatty acid consumption and cancer risk were reported for breast cancer in 4 studies[7,29,33,35]; for colorectal cancer in 1[5]; for lung cancer in 2[6,46]; for prostate cancer in 2[56,58]; and for skin cancer in 1.[59] However, for each breast, lung, and prostate cancer, there were significant associations for both increased risk and decreased risk and far more estimates that did not demonstrate any association. The study that assessed skin cancer risk found a significantly increased risk.[59] Hence, no trend was found across many different cohorts and many different categories of omega-3 fatty acid consumption to suggest that omega-3 fatty acids reduce overall cancer risk.

Considering these data together, there is no overall trend across different cohorts and categories of omega-3 fatty acid consumption to suggest that omega-3 fatty acids reduce overall cancer risk; that is, 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. Likewise, there is little to suggest that omega-3 fatty acids reduce the risk of any single type of cancer. Although risk reductions were observed for breast, colorectal, lung, and prostate cancer, the majority of other studies for these types of cancer, found no association. Indeed, for each breast, lung, and prostate cancer, there were studies that reported an increased risk of cancer. 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.

In considering the data, the relative strength of the data presented by individual studies should be considered in terms of methodological quality and sample size. All studies that entered this analysis were prospective in design and reported methodological attributes suggestive of high methodological quality (Table 1). The sample size was large in each of the studies, ranging from 6000 to 121 000. Although quantitative methods to evaluate the effect of sample size on overall risk were not used in this analysis as a result of substantial heterogeneity across studies, qualitative evaluation of the data does not suggest differences in reported risks based on sample size. Indeed, across all studies and across studies for each type of cancer, those with the largest sample size report no association between omega-3 fatty acids and cancer risk. Visual inspection of Figure 2 and Figure 3 demonstrates that risk estimates for the studies with the smallest variance, ie, the largest studies, are generally at or near the null value. Studies for which the magnitude of the reported risk ra-

tio (positive or negative) was large and generally had large variance and small sample size.

The apparent absence of an association between omega-3 fatty acid and the incidence of cancer in humans appears to contrast with the findings from studies of laboratory animals and in vitro studies. Reviews of studies in laboratory animal and in vitro models generally report small but significant suppressive effects of dietary n-3 fatty acid on the incidence, growth rate, or proliferation of mammary, prostate, colon, and pancreatic tumors.[23] However, several factors make it unclear how much light these results shed on the development or progression of cancer in humans. First, the models used to conduct these studies do not come close to replicating human exposures and have not yet succeeded in elucidating the mechanisms by which omega-3 fatty acids might be exerting their effects, not to mention the stage of tumor development. Second, the methods used to modify dietary omega-3 fatty acid composition in the animal models are controversial.[23] Because they generally consist of varying the ratio of omega-3 to omega-6 fatty acids or simply supplementing a commercial diet with omega-3 fatty acids (usually in the form of fish oil), it is impossible to assess whether positive findings are attributable to increased exposure to omega-3 fatty acids, decreased exposure to omega-6 fatty acids, or some other effect such as the decreased caloric intake that might result from decreased dietary palatability, since these studies almost always provide food ad lib and seldom measure intake. An additional concern is that the high doses of omega-3 fatty acid frequently used in animal studies could produce bleeding if administered to humans.[23]

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 fatty acid consumption varied a great deal across study cohorts. However, given that basically no effect was found in any of the cohorts, this difference could be regarded as evidence that omega-3 fatty acids have no effect regardless of intake. 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 known whether omega-3 fatty acid consumption remained constant over the observation period for ascertainment of cancer incidence, which ranged from 1 to 27 years. Thus, the reported estimates of effect for these studies should be interpreted with caution.

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 article were all essentially negative, publication bias does not appear to be present.

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. However, it is unlikely that our data were incomplete, given that our screening strategy was broad and that among the more than 1200 articles that were of possible relevance to the report only 36 could not be located.

A large body of literature spanning numerous cohorts from many countries and with different demographic characteristics did not provide evidence to suggest a significant association between omega-3 fatty acids and cancer incidence. Dietary supplementation with omega-3 fatty acids is unlikely to reduce the risk of cancer.

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CORRECTIONS

Data Error: In the Original Contribution entitled "Development and Validation of a Prognostic Index for 4-Year Mortality in Older Adults" published in the February 15, 2006, issue of *JAMA* (2006;295:801-808), a data error was published. In the Box, the number of points assigned for diabetes should have been 1.

Incorrect Study Listed: In the Review Article entitled "Effects of Omega-3 Fatty Acids on Cancer Risk: A Systematic Review" published in the January 25, 2006, issue of *JAMA* (2006;295:403-415), a study was incorrectly identified. In Figure 2, in the "Prostate" cancer section, the "Swedish Women,[42] 2001" entry should read "Swedish Twin Registry,[56] 2001."

Incorrect Data: In the Original Contribution entitled "Operating Characteristics of Prostate-Specific Antigen in Men With an Initial PSA Level of 3.0 ng/mL or Lower" published in the July 6, 2005, issue of *JAMA* (2005;294:66-70), the data in the "Race" section of **TABLE 1** were incorrect. These data should have read as follows:

Table 1. Characteristics of Participant Population

	No. (%)	
	Verified (n = 5587)	Unverified (n = 2988)
Race		
White	5341 (95.6)	2775 (92.9)
African American	176 (3.2)	139 (4.7)
Other	70 (1.3)	71 (2.4)
Missing	0	3 (0.1)