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Fish-Derived Omega-3 Fatty Acids and Prostate Cancer: A Systematic Review

Monique Aucoin, ND[1], Kieran Cooley, ND[1], Christopher Knee, ND, MSc[1], Heidi Fritz, ND, MA[1], Lynda G. Balneaves, RN, PhD[2], Rodney Breau, MSc, MD, FRCSC[3], Dean Fergusson, MHA, PhD[4], Becky Skidmore, MLS[1], Raimond Wong, MD, FRCSC[5], and Dugald Seely, ND, MSc, FABNO[1,4,6]

Abstract

Background. The use of natural health products in prostate cancer (PrCa) is high despite a lack of evidence with respect to safety and efficacy. Fish-derived omega-3 fatty acids possess anti-inflammatory effects and preclinical data suggest a protective effect on PrCa incidence and progression; however, human studies have yielded conflicting results. *Methods*. A search of OVID MEDLINE, Pre-MEDLINE, Embase, and the Allied and Complementary Medicine Database (AMED) was completed for human interventional or observational data assessing the safety and efficacy of fish-derived omega-3 fatty acids in the incidence and progression of PrCa. *Results*. Of 1776 citations screened, 54 publications reporting on 44 studies were included for review and analysis: 4 reports of 3 randomized controlled trials, 1 nonrandomized clinical trial, 20 reports of 14 cohort studies, 26 reports of 23 case-control studies, and 3 case-cohort studies. The interventional studies using fish oil supplements in patients with PrCa showed no impact on prostate-specific antigen levels; however, 2 studies showed a decrease in inflammatory or other cancer markers. A small number of mild adverse events were reported and interactions with other interventions were not assessed. Cohort and case-control studies assessing the relationship between dietary fish intake and the risk of PrCa were equivocal. Cohort studies assessing the risk of PrCa mortality suggested an association between higher intake of fish and decreased risk of prostate cancer–related death. *Conclusions*. Current evidence is insufficient to suggest a relationship between fish-derived omega-3 fatty acid and risk of PrCa. An association between higher omega-3 intake and decreased PrCa mortality may be present but more research is needed. More intervention trials or observational studies with precisely measured exposure are needed to assess the impact of fish oil supplements and dietary fish-derived omega-3 fatty acid intake on safety, PrCa incidence, treatment, and progression.

Keywords

fish oil, omega-3, fish, prostate cancer, prostate carcinoma, PSA

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Introduction

Prostate cancer (PrCa) accounts for almost one quarter of cancers diagnosed among men. In Canada, there are approximately 24 000 new cancer cases (24% of all new male cancer cases) expected in 2015.[1] While 5-year survival rates have dramatically improved, PrCa is still the third leading cause of cancer death among men, with nearly 4000 deaths (10.1% of all male cancer deaths) expected in 2015 in Canada.[1] However, PrCa incidence and mortality varies 60-fold globally, with a dramatic increase observed in immigrants moving from low- to high-risk countries, suggesting that dietary and lifestyle factors play a role in its etiology and pathogenesis.[2] With Canadian men having approximately a 1 in 8 (12.8%) lifetime probability of being diagnosed with prostate cancer, there is strong interest in dietary and natural health product (NHP)

[1]Canadian College of Naturopathic Medicine, Toronto, Ontario, Canada
[2]University of Toronto, Toronto, Ontario, Canada
[3]Ottawa Hospital General Campus, Ottawa, Ontario, Canada
[4]Ottawa Hospital Research Institute, Ottawa, Ontario, Canada
[5]McMaster University, Hamilton, Ontario, Canada
[6]Ottawa Integrative Cancer Centre, Ottawa, Ontario, Canada

Corresponding Author:
Dugald Seely, Ottawa Integrative Cancer Centre, 29 Bayswater Avenue, Ottawa, Ontario, K1Y 2E5 Canada.
Email: dseely@ccnm.edu

interventions, which may be effective in either the prevention or treatment of PrCa.

There is widespread evidence that many patients with PrCa take NHPs, frequently without any clinical supervision. Surveys conducted in the United States, Britain, Australia, and Canada suggest that complementary and alternative medicine (CAM) is widely used among prostate cancer patients; with estimates of CAM prevalence between 25 to 90%[3-7] and rates of disclosure to the patient's physician or oncologist as low as 25%.[8]

Fish-derived omega-3 fatty acids have emerged as a topic of interest in the prevention and treatment of PrCa. The omega-3 fatty acids found in fish include eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). These fatty acids exhibit anti-inflammatory properties through their impact on prostaglandin synthesis.[9] Populations with a high consumption of fish, such as those in Japan and Alaskan Inuit, have lower rates of PrCa than populations who consume the more typical Western diet, where intake of fish and the anti-inflammatory fish-derived omega-3 fatty acids is generally lower,[2] and intake of pro-inflammatory omega-6 fatty acids is generally much higher.[10] Additionally, a wide range of mechanisms by which omega-3 fatty acids affect cancer development have been elucidated[11] and a large number of in vitro and animal studies show that EPA and DHA have inhibitory effects on PrCa growth and progression.[12-17] Briefly, some of the chief mechanisms of action behind the cancer modulating effects of fish oil include the following: suppression of raft-associated signal transduction, promotion of BAD-dependent apoptosis via the PI3K/AKT survival pathway (phosphatidylinositol 3-kinase and serine/threonine protein kinase AKT), reduction of oxidative stress-induced endothelial Ca^{2+} influx via transient receptor potential channels (TSPs) and nuclear factor erythroid-2-related factor 2 (Nrf2) activation, and resolution of inflammation through the action of E-resolvins (RvE1 and RvE2), D-resolvins (RvD1 and RvD2), and protectin (PD1) on cyclooxygenase (COX) and lipoxygenase (LOX) pathways.[18]

The clinical potential of omega-3 fatty acids in the context of PrCa prevention and treatment remains controversial, and the results of numerous randomized controlled trials (RCTs), case-control studies, epidemiological reports, and systematic reviews assessing the role of fish-derived omega-3 fatty acids in the incidence and progression of PrCa have been largely inconsistent. The equivocal results are complicated by high variability in study methodology in terms of measurements of exposure (eg, food frequency questionnaires [FFQ]; plasma, serum or prostate tissue fatty acid levels); PrCa outcomes (eg, incidence, mortality, or progression) and biomarkers (eg, prostate-specific antigen [PSA] or inflammatory markers such as cyclooxygenase-2) used to assess fish-derived omega-3 fatty acid status and clinical outcomes.

To our knowledge, there are no evidence-based guidelines currently available for patients or clinicians indicating whether fish-derived omega-3 fatty acids are safe or effective in the context of PrCa treatment, progression, and prevention. In the absence of guidelines, men often self-prescribe based on limited information found on the Internet or obtained from family and friends.[19]

Patients and clinicians need to have access to reliable, credible, and evidence-based information about potential risks and benefits when making decisions about using NHPs in the context of PrCa. Because previous studies have reported mixed or conflicting result on the relationship between fish-derived omega-3 fatty acid and PrCa, thorough analysis of the entire body of literature is warranted. Therefore, we performed a systematic, evidence-based review of the available literature regarding fish-derived omega-3 fatty acids for the treatment and prevention of PrCa, with the purpose of developing comprehensive knowledge translation tools for oncology health professionals and, ultimately, patients with PrCa.

Methods

Methods of the analysis and inclusion criteria were specified in advance and documented in a registered protocol (PROSPERO 2014:CRD42014013014).[20]

Search Strategy

Electronic search strategies were developed by an experienced medical information specialist in consultation with the review team (Appendix A). Using the OVID platform, we searched OVID MEDLINE, Pre-MEDLINE, Embase, and the Allied and Complementary Medicine Database (AMED). We also searched the Cochrane Library on Wiley and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) on EBSCO and 2 Chinese-language databases (Wanfang and China National Knowledge Infrastructure databases). All database searches were performed on July 21, 2014 and updated June 21, 2015. Searches included controlled vocabulary terms (eg, "Prostatic Neoplasms," "Fatty Acids, Omega-3," "Docosahexaenoic Acids") and key words (eg, prostate cancer, Omega 3, PUFAs). There were no language or date restrictions on any of the searches. ClinicalTrials.gov and the International Clinical Trials Registry Platform (ICTRP) were searched for current and completed clinical trials.

Inclusion Criteria

Eligible studies assessed male patients of any age for primary or secondary prevention or progression of PrCa. The studies assessed, used, or measured dietary and/or supplemental intake of fish-derived omega-3 fatty acids with or without other supplements or measured the omega-3 content

in biological samples obtained from participants. Studies assessing non–fish-derived omega-3 fatty acids such as alpha-linoleic acid or flaxseed oil were excluded. Studies using placebos, comparator groups consisting of natural or pharmacological agents, or no control were eligible. Eligible study designs included RCTs, non–randomized controlled trials (non-RCTs), and observational studies (case-control, cohort) but not preclinical or cross-sectional studies.

Record Screening and Selection

All citations identified by the systematic search were downloaded into a reference database. Two investigators independently reviewed all identified titles and abstracts for eligibility. Disagreement regarding inclusion of records was determined by consensus and third party arbitration by another member of the research team, when appropriate. Duplicate reports of studies were included.

Data Extraction

Data were extracted independently by 2 investigators using data abstraction sheets that had been developed and piloted among the investigative team. Outcome measures extracted included relative risk (RR), hazard ratio (HR), and odds ratio (OR). Outcome measures that were adjusted for known PrCa risk factors such as age, ethnicity, family history, smoking status, and body mass index (BMI) were extracted when available. When not reported, unadjusted outcomes were extracted. Study authors were contacted to clarify results reported in 2 publications[21,22]; however, no new information was obtained.

Outcomes

The primary outcome of this review is primary prevention of PrCa. Secondary outcomes include PSA level, PSA doubling time, Gleason score, recurrence, tumor response rates, survival, immune function (clinical or surrogate parameters), quality of life (QOL), other cancer symptoms or chemotherapy-related side effects, adverse events/toxicities, the Eastern Cooperative Oncology Group (ECOG) and/or Karnofsky performance scores, Edmonton Symptom Assessment Scale (ESAS), prognostic scores (Glasgow PS), or other cancer markers or relevant surrogates. Additionally, we assessed for interactions, defined as a pharmacological or clinical responses to the administration or co-exposure of a treatment and another substance that modifies either the effectiveness or safety of the treatment.[23,24]

Exposure

Data on the dose of fish-derived omega-3 fatty acid intake were extracted from the studies. When these data were not reported as mg of EPA + DHA per day, a conversion was performed to create a standardized dose by weight. To facilitate conversion when intake was reported in servings of fish, a standard of 0.798 g EPA + DHA per servings of fish was used. This was calculated by finding the average EPA + DHA content among the different fish and seafood types listed in the Dietitians of Canada online reference.[25] When intake of fatty acids was reported as a percentage of daily caloric intake, a standard of 2350 calories per day was utilized based on the Health Canada Food Guide recommendations for adult men with low activity level. The percentage was multiplied by 2350 calories and divided by 9 cal/g to approximate the grams of fish oil taken in per day.

Risk of Bias Assessment

The quality of clinical trials was assessed using the Cochrane Risk of Bias tool.[26] The quality of cohort and case-control studies was assessed using the Newcastle-Ottawa Scale.[27] All studies were assessed for their source of funding (industry vs nonindustry). Assessment was completed independently by 2 investigators and disagreement was resolved by consensus or third party arbitration, when appropriate. For nonrandomized trials, we assessed quality according to reporting of blinding of patients and assessors, a priori sample size estimation and low loss to follow-up (<20%).

Data Analysis

Analysis was completed separately for each type of study design. A random-effects model was used to pool results from the studies, including the following measures of effect and 95% confidence intervals (CIs): RR, HR, and OR. When available, adjusted measures of effect were used. Forest plots were created to display the results for different types of studies that were pooled. When available, the effect of total fish-derived omega-3 fatty acids on total incidence of cancer was utilized. When these statistics were not available, other statistics were reported, such as the effect of EPA only and DHA only on PrCa risk or the effects of omega-3 fatty acids on advanced and nonadvanced PrCa. Additional forest plots were created to display the effects of fish-derived omega-3 fatty acid son PrCa mortality, to compare analyses of EPA alone to DHA alone and to compare studies utilizing different methods of assessing fish-derived omega-3 fatty acid exposure.

Planned sensitivity analyses included an assessment of the effect of methodological quality of included trials, withdrawals/losses to follow-up, and funding source, when feasible. Homogeneity was assessed using the I-squared statistic and the Zalen test. If some degree of homogeneity existed ($I^2 < 75\%$), a meta-regression analysis (using STATA) was conducted to determine the extent to which factors contributed to heterogeneity. Variable coefficients

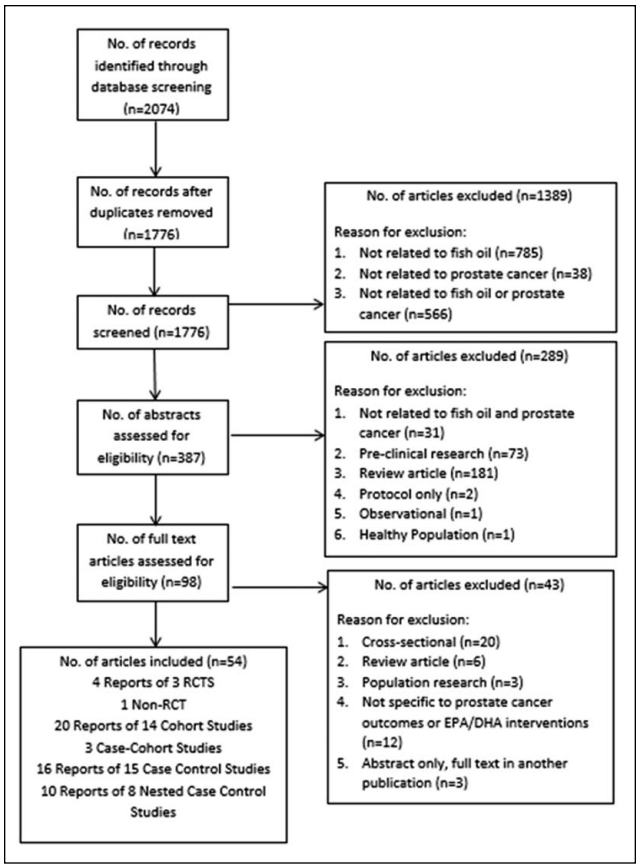


Figure 1. Literature flowchart.

are displayed in the beta-coefficient with 95% CIs and appropriate ORs with *P* values. A funnel plot test, using Eggers test for publication bias, was used to assess the likelihood of publication bias. Both quantitative (meta-analysis) and qualitative narrative synthesis of studies (based on study design) were planned.

Results

Of 1776 records screened, 54 publications, reporting on 44 studies, were included for review and analysis. Figure 1 shows a flowchart of the literature search and study selection. Search of the Chinese databases yielded 17 records, none of which met criteria for inclusion. Data extraction by 2 reviewers was found to have a high degree of agreement and consensus was reached on all articles. Meta-analysis was not completed due to the significant heterogeneity in the observational data and limited amount of interventional data. The results reported in the studies found were predominantly focused on cancer prevention. Eight publications reported on disease management and progression.[28-35] Many of the secondary outcomes that were planned in this review were not assessed by any of the included studies.

Interventional Studies

Five publications[28-32] reported on the results of 4 clinical trials, including 1 non-RCT (Table 1). Of the 4 trials, 1 was in patients with localized PrCA preprostatectomy,[29] 1 in patients undergoing active surveillance,[31] 1 in postprostatectomy patients,[28] and 1 in patients with untreated localized or regional PrCA.[32] Interventions included a low-fat diet plus fish oil supplementation (2400-5500 mg per day of fish oil providing 1600 to 2400 mg of EPA + DHA). PSA levels remained unchanged in all four trials (Table 1). Many reported a lack of significant effect on inflammatory markers; however, there were significant reductions in malignant epithelial cell proliferation (Ki-67) in one of the trials (decrease of 32.2% $P < .05$)[29] and decreased cell-cycle progression score, pro-inflammatory fatty acids 15-*S*-hydroxyeicosatetraenoic acid and leukotriene B4 in another study[30] (Table 1). The intervention studies analyzed were of short duration. Three of the 4 trials were three months or shorter in duration[29,31,32] and the remaining study was 2 years.[28]

Observational Evidence

Prospective Cohort Studies of Primary Prevention. Seventeen publications reported on 11 cohort studies investigating primary prevention of PrCA (Table 2). These studies assessed dietary fish-derived omega-3 fatty acids and supplementary fish oil intake (13 assessed diet alone, 1 assessed supplement intake alone, and 3 assessed both diet and supplement intake) and assessed incidence and mortality of PrCa over an average of 12.2 years (range 4-23.5 years). One additional study discussed in the nested case-control section of this review contained a prospective cohort component[36] that assessed the relationship between dietary intake and supplemental fish oil and the relationship with prostate cancer. In the studies assessing dietary intake, the highest quartile or quintile of intake was compared with the lowest, which included individuals who consumed very little or no dietary fish. Sixteen publications reported on the association of fish-derived omega-3 fatty acid intake with PrCa incidence. Of these, 3 studies[10,21,36] reported on advanced and nonadvanced prostate cancer separately resulting in a total of 19 analyses. The publications reported RR or HR and 12 publications reported outcomes that had been adjusted for other factors.

Of the 19 analyses assessing PrCa incidence, 12 did not show a statistically significant association.[10,21,37-44] Five analyses showed a significant association between increased intake of fish-derived omega-3 fatty acids and decreased PrCa incidence.[36,45-48] In 2 of these studies, the authors concluded that statistical significance was achieved based on the *P* value despite nonsignificant 95%Cis.[45,46] Two analyses reported a significant association between increased intake and increased PrCa risk.[36,49] In a subanalysis, another study demonstrated a positive association (ie, increased PrCa)

Table 1. Characteristics of Human Trials Investigating Supplemental Fish-Derived Omega-3 Fatty Acids in Patients With Prostate Cancer.

Ref	n	Random	Control	Blind	PrCa Status; Other Treatments	Intervention	Duration (Months)	Effect of Intervention on PSA	Effect on Inflammatory Markers	Effect on Additional Outcomes
Randomized clinical trials										
Higashihara et al (2010)[28]	62	Yes	No Tx	NR	PrCa PSA < 0.2 ng/mL 3 months postprostatectomy; None	2400 mg/d EPA ethyl ester	48	Equal PSA failure rate (4 in EPA group, 8 in placebo; Kaplan-Meier $P = .16$)		
Aronson et al (2011)[29]	48	Yes	Western diet (15:1 n-6:n-3 ratio), no placebo	Single	Localized PrCa preprostatectomy; scheduled for surgery in ≥4 weeks	Low-fat diet + 5.5 g/d FO (1835 mg DHA, 1000 mg EPA); 2:1 n-6:n-3 ratio	1-1.5	↔ PSA (change of 0.08 ± 0.4 mg/mL vs −0.09 ± 0.3 $P = .53$)	↔ serum IGF-1 ($P = .25$) ↔ serum IGFBP-1 ($P = .84$) ↔ serum IGFBP-3 ($P = .14$) ↔ urine PGEM ($P = .36$) ↔ Pr tissue PGE2 ↔ COX-2	↓ malignant epithelial cell proliferation (Ki67) by 32.2% ($P < .05$) ↓22RV1 cell proliferation (−5.0% ± 1.8% vs 0.6% ± 1.9% $P = .039$) ↔ angiogenesis, apoptosis immunostaining
Galet et al (2014)[30]; post hoc analysis of Aronson et al (2011)[29]	As Aronson 2011								↓ 15(S)-HETE (−7.2 ± 6.6 vs 24.7 ± 11.4 in placebo $P = .02$) ↓ LTB4 post-LFFO vs pre-LFFO, but ↔ relative to control (14.9 ± 5.6 vs −9.7 ± 7.4 in placebo)	↓ cell-cycle progression score ($P = .03$)
Chan et al (2011)[31]	69	Yes	Placebo	Double	Low-grade PrCa; active surveillance	3 g/d FO (1098 mg EPA, 549 mg DHA)	3	↔ PSA (change of 0.20 ng/mL vs −0.46 $P = .39$)	↔ in COX-2 expression (change of 0.39 ± 1.98 vs 0.40 ± 2.19 in placebo)	
Nonrandomized clinical trial										
Aronson et al (2001)[32]	9	No	N/A	N/A	Untreated localized or regional PrCa; none	Low-fat diet + 3 g/d FO (1800 mg EPA, 1200 mg DHA) + 800 IU vit E	3	↔ PSA (baseline: 11.15 ± 2.9 ng/mL), final: 13.12 ± 4.0	↓ COX-2 in 4 of 7 patients compared with baseline (not statistically powered to detect)	

Abbreviations: PrCa, prostate cancer; n-3, omega-3 fatty acid; n-6, omega-6 fatty acid; N/A, not applicable; NR, not reported; FO, fish oil; LFFO, low-fat diet + fish oil; Tx, treatment; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; PSA, prostate-specific antigen; IGF-1, insulin-like growth factor 1; IGFBP-1, insulin-like growth factor binding protein 1; IGFBP-3, insulin-like growth factor binding protein 3; PGEM, prostaglandin E2 metabolite; PGE2, prostaglandin E2; COX-2, cyclooxygenase-2; Pr, protein; CHO, carbohydrate; vit, vitamin; FA, fatty acid; ↔, no change; ↑, increase; ↓, decrease.

Table 2. Prospective Cohort Studies of Dietary and Supplemental Fish-Derived Omega-3 Fatty Acids and Risk of Primary Prostate Cancer.

Reference	Cohort/ Study Name	Cohort n	Cases n	Geographic Area	PrCa Status at Baseline; Other Tx	Exposure Assessment	Years f/u	Highest group (quartile, quintile, etc.); Dose	Effect of exposure on outcome (highest vs. lowest exposure)
Allen et al (2004)[49]	Life Span Study	18 115	196	Hiroshima or Nagasaki, Japan	No evidence of disease	FFQ	16.9	Eating fish almost daily or more often; **684 mg/d**	↑ risk of PrCa RR 1.77 (1.01-3.11) *P* = .07
Augustsson et al (2003)[45]	Health Professionals Follow-Up Study	47 882	2482	USA	Never	FFQ	12	Eating fish more than 3×/wk; **342 mg/d**	↓ risk total PrCa mvRR 0.93 (0.80-1.08), advanced PrCa mvRR 0.83 (0.61-1.13), metastatic PrCa mvRR 0.56 (0.37-0.86)
								FO supp use	↔ risk of PrCa
Leitzmann et al (2004)[46]	Health Professionals Follow-Up Study	47 866	2965	USA	Never	FFQ and supplement inquiry	14	Dietary EPA + DHA >0.214% energy; **558 mg/d**	↓ risk of PrCa RR 0.89 (0.77-1.04) *P* = .002 ↔ fatal PrCa 0.68 (0.40-1.17) *P* trend = .12
								FO supp >2.5 g/d	↔ risk of PrCa mvRR 0.89 (0.62-1.30) *P* = .91
Giovannucci et al (1993)[37]	Health Professionals Follow-Up Study	47 885	300	USA	Never	FFQ	4	Median of 0.55 g/day n-3 fat (from fish); **550 mg/d**	↔ risk of PrCa RR 0.90 (0.51-1.61) *P* = .30
Bonner et al (2012)[47]	New York State Angler Cohort	17 110	58	USA	Never	Self-administered food questionnaire	17	Ever eaten fish from Lake Ontario (vs never)	↓ risk of PrCa RR 0.5 (0.3-0.8)
Brasky et al (2011)[50]	VITamins And Lifestyle (VITAL) Cohort	35 239	1602	USA	Never	Questionnaire of supplement use	6.1	User of fish oil supp (>1 d/ wk for >1 year)	↔ risk of PrCa mvHR 0.98 (0.82-1.17) *P* = .61
Daniel et al (2011)[39]	NIH-AARP Diet and Health Study	293 466	23 453	USA	Never	FFQ	9.1	21.4 g fish/1000 kcal; **535 mg/d**	↔ risk of PrCa HR 1.02 (0.98-1.06) *P* = .67
Pelser et al (2013)[10]	NIH-AARP Diet and Health Study	288 268	23 281	USA	Never	FFQ	9	EPA 0.036% energy	↔ risk of advanced/nonadvanced PrCa mvHR 0.93 (0.82-1.04) *P* = .15; mvHR 1.05 (1.00-1.10) *P* = .69 ↓ risk of fatal PrCa mvHR 0.82 (0.64-1.04) *P*trend = .02
								EPA + DHA 0.103% energy; **269 mg/d**	↔ risk of advanced (mvHR 0.97 (0.86-1.09) *P* = .31); nonadvanced (mvHR 1.04 (1.00-1.10) *P* = .45); or fatal PrCa (mvHR 0.87 (0.68-1.10) *P* = .10)
Bosire et al (2013)[51]	NIH-AARP Diet and Health Study	293 464	23 453	USA	Never	FFQ	8.9	>0.66 ounce/d of fish; **199 mg/d**	↓ risk of fatal PrCa mvHR 0.79 (0.65-0.96)
								≥250 mg/d marine n-3; **250 mg/d**	↓ risk of fatal PrCa mvHR 0.94 (0.90-0.98)
Terry et al (2001)[48]	N/A	6274	466	Sweden	Never	Self-administered food questionnaire	21.4	Fish accounted for "large part of diet"	↓ risk of PrCa mvRR 0.43 (0.22-0.83) *P* < .05; ↓ risk of PrCa death mvRR 0.30 (0.17-0.56) *P* < .01

(continued)

Table 2. (continued)

Reference	Cohort/ Study Name	Cohort n	Cases n	Geographic Area	PrCa Status at Baseline; Other Tx	Exposure Assessment	Years f/u	Highest group (quartile, quintile, etc.); Dose	Effect of exposure on outcome (highest vs. lowest exposure)
Crowe et al (2008)[40]	EPIC	142520	2727	10 European countries	Never	FFQ	8.7	Not defined	↔ risk of PrCa Total PrCa risk mvHR per 1% increase in energy from fish fat: 1.00 (0.93-1.07) *P* = .977 ↔ risk of localized, advanced, high-grade, or low-grade PrCa
Kristal et al (2010)[21]	Prostate Cancer Prevention Trial	9559	1703	USA and Canada	Never; Finasteride or placebo	FFQ and supplement questionnaire	7	Total EPA + DHA >0.28 mg/d; **0.28 mg/d**	↔ risk of PrCa For GS 2-7 OR 1.11 (0.94-1.31) *P* = .230 For GS 9-10 OR 1.46 (0.86-2.50) *P* = .193
Pham et al (2009)[52]	Miyako Study	5589	21 deaths	Japan	Never	Self-administered questionnaire	13.4	Fish consumed at least 2-4×/wk; **342 mg/d**	↓ risk PrCa death mvHR 0.12 (0.05-0.32)
Chavarro et al (2008)[41]	Physician's Health Study	20167	2162 cases, 230 deaths	USA	Never; aspirin and beta-carotene	FFQ	19	Fifth quintile of seafood n-3 FA intake	↔ risk of PrCa mvRR 1.09 (0.95-1.25) *P* = .55 ↓ risk of PrCa death mvRR 0.65 (0.42-0.99) *P* = .02
Sato et al (2008)[42]	Osaki National Health Insurance Subscribers Cohort Study	24895	95	Japan	Never	FFQ	7	Fish intake >100 g/d; **1064 mg/d**	↔ risk of PrCa; mvHR 0.72 (0.40-1.33) *P* = .23 Among >70-year-olds mvHR 0.44 (0.18-1.11) *P* = 0.08
Wallstorm et al (2007)[43]	Malmo Diet and Cancer Cohort	10564	817	Sweden	Never	Questionnaire (including Supplement) and Menu record	11	1.30 g/d of EPA + DHA supplement; **1300 mg/d**	↔ risk of PrCa mvRR 1.26 (1.00-1.59) *P* = .056
								0.47 g/d EPA	↑ risk of PrCa mvRR 1.30 (1.03-1.64) *P* = .043
								0.88 g/d DHA	↔ risk of PrCa mvRR 1.26 (1.00-1.59) *P* = .062
Chavarro et al (2010)[44]; full text not published	Physician's Health Study	488	94 Pr CA deaths	USA	Never	Blood FA levels at baseline	23.5	Quartiles of serum FAs	↔ risk of PrCa death (data not provided in abstract)
Torfadottir et al (2013)[36]	AGES-Reykjavik Cohort Study	133	1944	Iceland	Never	FFQ	7	Once a week or more intake of salted or smoked fish	↑ risk advanced PrCa intake later life OR 2.28 (95% CI: 1.04, 5.00) ↓ risk of localized PrCa intake later life AOR 0.63 (0.40-1.00)
								Fish oil use daily	↓ risk of advance PrCa HR 0.43 (0.19-0.95) with use in later life

Abbreviations: PrCa, prostate cancer; mvRR, multivariate relative risk; mvHR, multivariate hazard ratio; AOR, adjusted odds ratio; FFQ, Food Frequency Questionnaire; Tx, treatment; N/A, not applicable; ×/wk, times per week; f/u, follow-up; Bl, baseline; ↓, decrease; ↑, increase; ↔ no effect; GS, Gleason score; FO fish oil; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; n-3, omega-3; NR, not reported; Supp, supplement.

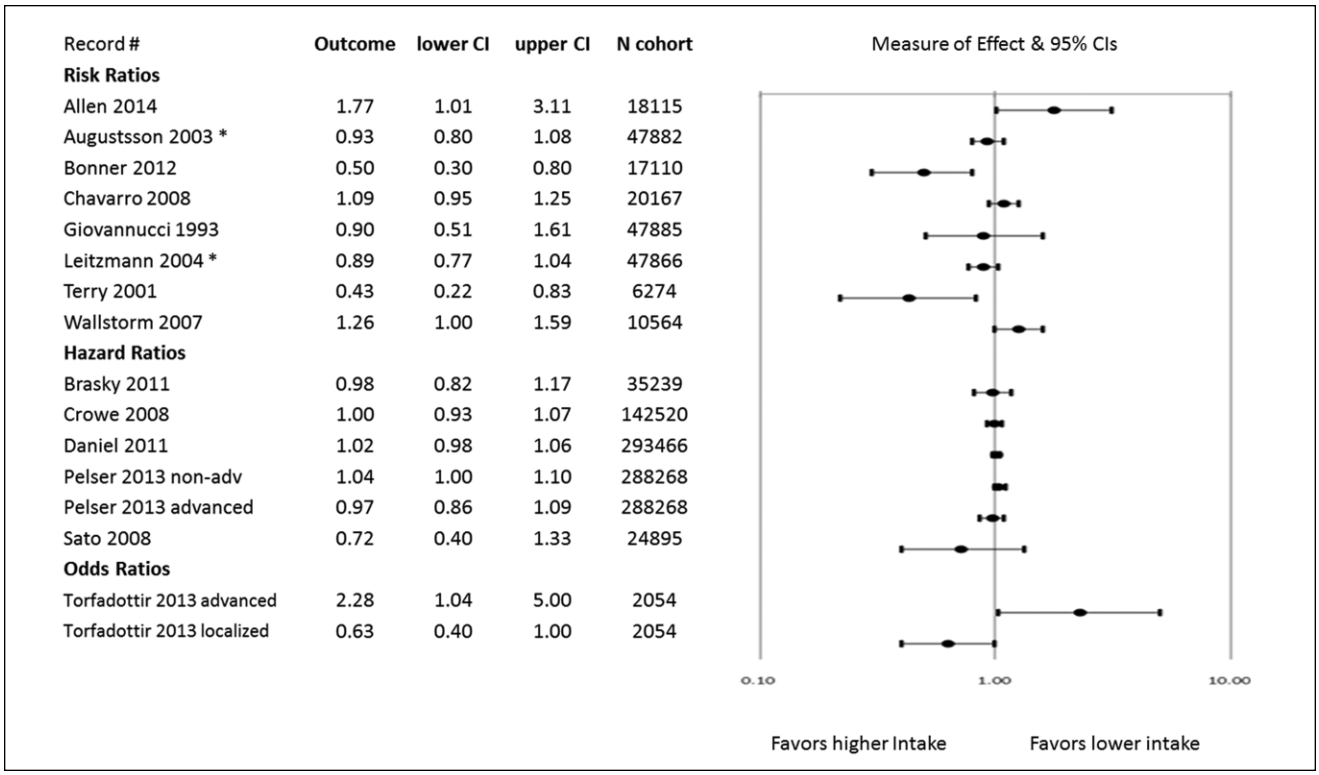


Figure 2. Risk of prostate cancer (PrCa) incidence with fish-derived omega-3 fatty acid intake: Prospective cohort studies. When the effect of fish-derived omega-3 fatty acid intake on total PrCa risk was not available, subanalyses reporting on different stages of cancer (eg, advanced cancer and nonadvanced cancer) are reported. *Study authors concluded that the results achieved statistical significance based on *P* value and confidence interval.

with increased EPA intake but not with increased intake of DHA or EPA + DHA.[43] The results of the primary cohort studies are presented in a forest plot (Figure 2); with the exception of 1 study where the data were not available.[44]

Five prospective cohort analyses assessed the impact of fish oil supplements (or the combination of diet and fish oil supplements in 1 study); 4 demonstrated no statistically significant association with the risk of PrCa incidence.[43,45,46,50] One demonstrated a relationship between daily supplemental fish oil intake in later life and a decrease in advanced PrCa incidence.[36]

Among the 7 cohort study reports assessing the risk of death related to PrCa, 5 studies reported a significant association between higher intake of fish-derived fatty acids and decreased risk of death.[35,41,48,51,52] Of the 2 remaining studies, one showed a significant association between decreased risk of death and higher EPA intake and a nonsignificant association with higher total EPA + DHA.[10] The remaining study showed an association between decreased risk of death and higher total EPA + DHA intake that approached significance.[46]

Prospective Cohort Studies of Secondary Prevention. Three publications reported on cohort studies assessing progression or risk of death among patients with PrCa (Table 3).[31,34,35] In these 3 studies, patients underwent conventional individualized treatment for their PrCa. One study measured the time to PrCa-related death[35] while one defined progression as either PrCa death, bone metastases from PrCa, biochemical recurrence, or initiation of secondary treatment.[34] The third study asked the patient's treating physician to whether or not the patient's prostate cancer had recurred or progressed since the initial treatment[33] and when not available defined progression as 2 or more successive rises in PSA, initiation of second therapy or positive scans for metastasis. Two studies utilized an FFQ to assess dietary fish intake after diagnosis of PrCa and analyzed risk of disease progression; no impact from high fish intake was found[33,34]. The third study assessed risk of PrCa death and found an association between lower risk and higher fish-derived omega-3 fatty acid intake in the year prior to diagnosis.[35]

The results of the primary and secondary cohort studies assessing risk of death are presented together in a forest plot (Figure 3).

Dose of Fish-Derived Omega-3 Fatty Acids. Among the cohort studies, the amount of fish-derived omega-3 fatty acid intake in the highest quartile of dietary intake varied widely,

Table 3. Prospective Cohort Studies of Dietary Fish-Derived Omega-3 Fatty Acids and Risk of Prostate Cancer Progression or Death.

Reference	Cohort/ Study Name	Cohort n	Cases n	Geographic Area	PrCa Status at Baseline	Study Objective	Exposure Assessment	Years f/u	Highest Exposure Group (Quartile, Quintile, etc); Dose	Effect of Exposure on Outcome (Highest vs Lowest Exposure)
Chan et al (2006)[31]	Health Professionals Follow-up Study	1202	392 cases progression	USA	Present	Prevent progression	FFQ of intake postdiagnosis	10	Not reported	↔ Risk of PrCa progression HR 0.73 (0.52-1.02)
Richman et al (2010)[34]	Cancer of the Prostate Strategic Urologic Research Endeavour (CaPSURE)	1294	127 cases progression	USA	Present (excluding advanced or metastatic)	Prevent progression	FFQ of intake postdiagnosis	2	Median 4.3 servings/wk; **490 mg/d**	↔ Risk of PrCa progression mvHR 1.13 (0.70-1.84)
Epstein et al (2012)[35]	N/A	525	222 cases of PrCa death	Sweden	Present	Prevent death due to PrCa	FFQ of intake 1 year prediagnosis	20	0.8 g marine FAs/ day; **800 mg/d**	↓ risk PrCa death HR 0.59 (0.4-0.87) $P = .04$

Abbreviations: PrCa, prostate cancer; mvRR, multivariate relative risk; mvHR, multivariate hazard ratio; AOR, adjusted odds ratio; FFQ, Food Frequency Questionnaire; ×/wk times per week; f/u follow-up; Bl, baseline; ↓, decrease; ↑, increase; ↔ no change; RBC, red blood cells; FA, fatty acids.

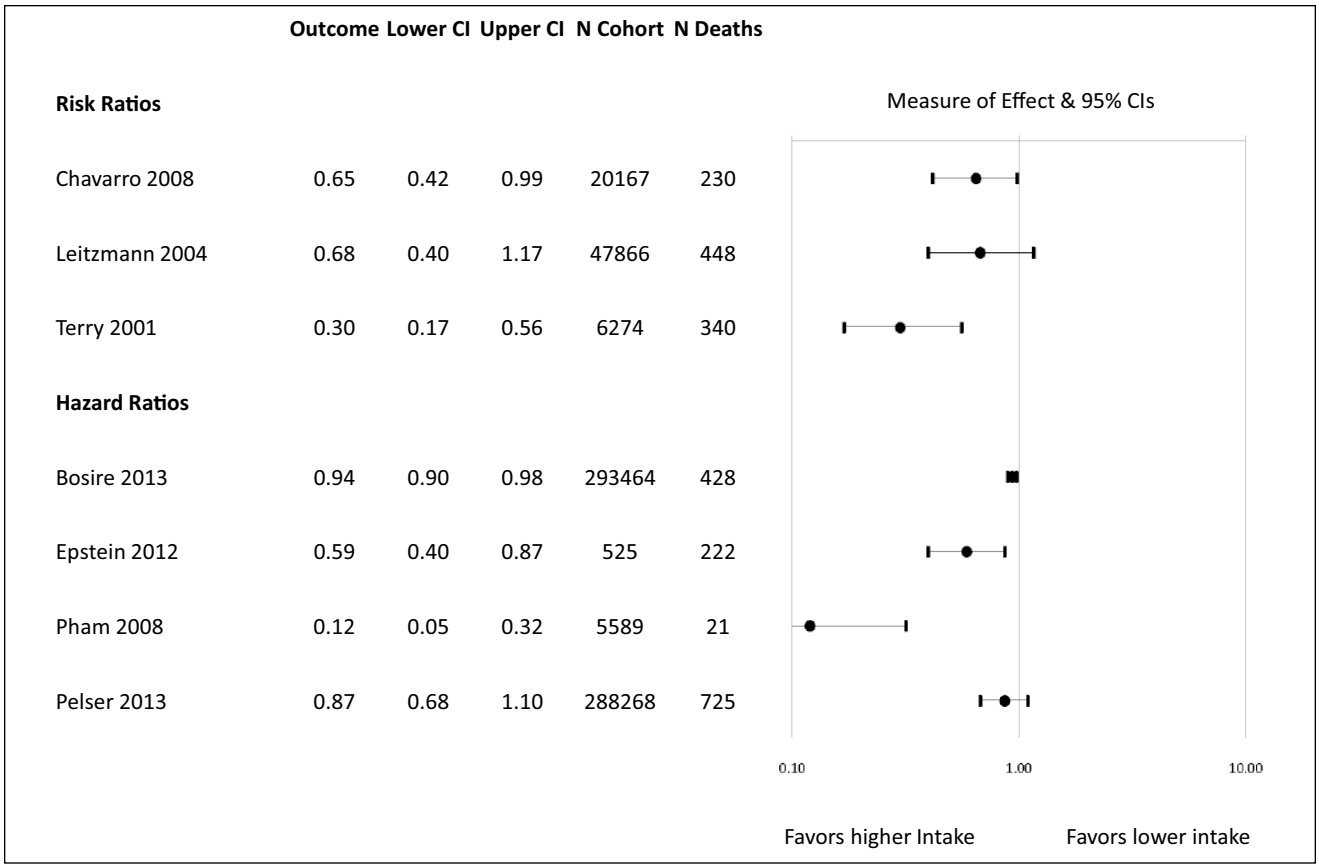


Figure 3. Risk of prostate cancer (PrCa) mortality with fish-derived omega-3 fatty acid intake: Prospective cohort studies case-cohort, case-control and nested case-control studies.

ranging from approximately 200 to 1300 mg/d of EPA + DHA (Table 2). No relationship between the dose of the exposure and study outcome was apparent. Individual studies reporting findings of increased risk of PrCA incidence, decreased risk of PrCA incidence, and no effect on risk of PrCA incidence had the following average intake of fish-derived omega-3 fatty acids in the highest quartile: 577, 373, and 666 mg, respectively.

Three case-cohort studies assessed the impact of fish intake on PrCa incidence (Table 4). Two studies showed no association between fish intake and PrCa.[53,54] One study showed no association between EPA intake and PrCa and a relationship between higher dietary intake of DHA and higher incidence of PrCa.[55]

Sixteen publications reported on 15 case-control studies and 10 publications reported on 8 nested case-control studies. These results are presented in Tables 5 and 6 and displayed in Figures 4 and 5. There was considerable heterogeneity in the results of the different studies as well as the methodology, analyses and reporting in individual studies. The studies varied in their method of assessing exposure, the time of exposure, the type of fish eaten and the marine fatty acids measured (EPA, DHA, EPA + DHA). Of the case-cohort, case-control, and nested case-control studies, 10 utilized whole blood, plasma, serum or RBC fatty acid analysis to assess fish-derived omega-3 fatty acid exposure, whereas 21 assessed intake through participant recall using a FFQ.

Among those that assessed fish-derived omega-3 fatty acid intake through recall with significant findings, 8 analyses showed an association between higher intake and lower risk of PrCa incidence[56-61] while 4 analyses showed an association with higher risk of incidence.[36,61-63] Among the studies that assessed blood levels, 3 analyses reported an association between higher intake and lower risk[22,41] and 5 reported an association with higher risk of incidence.[40,50,55,64,65] Among the studies reporting an association between higher fish intake on recall and higher risk, the type of fish intake assessed was related to the outcome. One study showed an association with increased risk with higher intake of cod, saithe, shellfish, and "fish fingers" but an association with decreased risk with higher intake of salmon-type fish while adjusting for intake of the other fish types.[61] It also showed that when overall intake of EPA + DHA was assessed, the effect was protective. Another study showed an association with increased risk with higher white fish intake (unadjusted

Table 4. Case-Cohort Studies of Fish-derived omega-3 fatty acids and Prostate Cancer Incidence.

Reference	Cohort/Study Name	Cases n	Controls n	Geographic Area	Exposure Assessment	Highest Group (Quartile, Quintile, etc)	Effect of Exposure on Outcome (Highest vs Lowest Exposure)
Assessing blood levels of fatty acids							
Bassett et al (2013)[53]	Melbourne Collaborative Cohort Study	464	1717	Australia	PPL FAs and FFQ at baseline	Quintiles %PPL EPA and DHA (not defined)	↔ risk of PrCa EPA mvHR 1.05 (0.93-1.18) *P* = .42; DHA mvHR 0.99 (0.88-1.11) *P* = .86
						Dietary intake quintiles (not defined)	↔ risk of PrCa EPA mvHR 0.79 (0.56-1.12) *P* = .53; DHA mvHR 0.878 (0.61-1.25) *P* = .52
Brasky et al (2013)[55]	SELECT Trial	834	1393	USA, Canada, Puerto Rico	Serum PPL at baseline	EPA >0.82% total FAs	↔ risk of total, low-grade or high-grade PrCa
						DHA >3.62% total FAs	↑ Total PrCa and low-grade PrCa DHA mvHR 1.39 (1.06-1.82) *P* = .009; mvHR 1.42 (1.06-1.89) *P* = .08 ↔ risk of high-grade PrCa with DHA
Assessing dietary intake of fatty acids							
Schuurman et al (1999)[54]	The Netherlands Cohort Study	642	1525	Netherlands	FFQ at baseline of cohort study	EPA intake 0.10 g/d DHA intake 0.18 g/d	↔ PrCa risk for EPA RR 1.00 (0.73-1.35) *P* = .10 and DHA RR 1.03 (0.75-1.40) *P* = .19

Abbreviations: PPL, plasma phospholipid; FA, fatty acids; PrCA, prostate cancer; mvRR, multivariate relative risk; mvHR, multivariate hazard ratio; FFQ, Food Frequency Questionnaire; ↓ decrease, ↑ increase, ↔ no effect; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid.

Table 5. Case Control Studies of Fish-derived omega-3 fatty acids and Prostate Cancer Incidence.

Reference	Cohort/ Study Name	Cases n	Controls n	Geographic Area	Exposure Assessment	Highest Group (Quartile, Quintile, etc)	Effect of Exposure on Outcome (Highest vs Lowest Exposure)
Assessing blood levels of fatty acids							
Ukoli et al (2010)[64]	N/A	48 African American, 66 Nigerian	125 African American, 274 Nigerian	Nigeria/USA	FFQ and plasma FA	Quartiles of plasma FA (not defined)	In African Americans: ↑ PrCa risk, Q3 vs Q1 DHA OR 6.63 (2.02-21.77) *P*trend < .004 ↔ PrCa risk Q4 vs Q1 DHA OR 1.35 (0.40-4.61)
Cheng (2013)[81]	Carotene and Retinol Efficacy Trial (CARET)	458	1369	USA	Serum PPL FA at baseline	Quartiles of serum EPA + DHA (not defined)	↔ risk of nonaggressive PrCa EPA + DHA mvOR 1.14 (0.80-1.63) *P* = .45 ↔ risk of aggressive PrCa mvOR 1.05 (0.71-1.55) *P* = .53
Assessing dietary intake of fatty acids							
Vlajinac et al (2010)[62]	N/A	101	202	Serbia	150-item FFQ	Tertiles and terciles of average daily intake (not defined)	↑ PrCa risk OR 2.60 (1.45-4.65) p<0.01 (mostly canned/processed)
Williams (2011)[82]	N/A	79	187	Virginia	Harvard 12-month FFQ	EPA 0.079-0.83% and DHA 0.10% to 0.64% (of total energy)	↔ PrCa risk EPA OR 1.13 (0.56-2.24) *P* = .73 DHA 0.82 (0.40-1.68) *P* = .6
Mina et al (2008)[60]	National Enhanced Cancer Surveillance System (NECSS)	1534	1607	Canada	60-item FFQ	Fresh/canned fish ≥2 servings /wk	↔ PrCa risk AOR 1.10 (0.84-1.42)
						Preserved (smoked/dried/ salted fish) ≥1 serving / wk	↓ PrCa risk 1-3 servings/mo preserved fish (vs 0/mo) AOR 0.78 (0.64-0.95)
Hu et al (2008)[69]	National Enhanced Cancer Surveillance System (NECSS)	1799	5039	Canada	Self-administered 69-item FFQ for previous 2 years	≥5 ounce fish/wk	↔ PrCa risk OR 0.8 (0.7-1.0) *P* = .08
Hedelin et al (2007)[61]	Cancer Prostate in Sweden (CAPS) Study	1499 (diet only), 1378 with blood samples	1130 (diet only), 782 with blood samples	Sweden	Self-administered 261-item 12-month FFQ	≥1 serving/wk	Salmon-type: ↓ PrCa risk OR 0.57 (0.43-0.76) Cod/saithe/fish fingers: ↑ PrCa risk OR 1.45 (1.12-1.88) Shellfish:↑ PrCa risk OR 0.81 (1.28-2.56)
						0.11 g EPA + DHA/day-MJ	↓ PrCa risk OR 0.70 (0.51-0.97)
Chen (2005)[83]	N/A	237	481	Taiwan	Interviewed FFQ for previous 10 years	Intake of "more" compared with others	↔ PrCa risk AOR 1.12 (0.80-1.56)
Sonoda et al (2004)[56]	N/A	140	140	Japan	Interviewed 102-item FFQ for previous 5 years	≥130.7 g/d fish intake	↓ PrCa risk OR 0.45 (0.20-1.02) *P* = .04
Pawlega et al (1996)57	N/A	76	152	Cracow, Poland	Self-administered 44-item FFQ for previous 20 years	Fish consumption ≥once/ wk vs <rarely	↓ PrCa risk smoked fish OR 0.5 (0.2-0.8) *P* < .05 ↓ PrCa risk fried fish 0.5 (0.2-0.9) *P* < .05
Talamini et al (1992)[68]	N/A	271	685	Northern Italy	Interviewed 14-item FFQ for preceding year	Fish intake ≥2 servings/wk	↔ PrCa risk OR 0.79 (0.53-1.17) *P* = .36

(continued)

Table 5. (continued)

Reference	Cohort/ Study Name	Cases n	Controls n	Geographic Area	Exposure Assessment	Highest Group (Quartile, Quintile, etc)	Effect of Exposure on Outcome (Highest vs Lowest Exposure)
Deneo-Pellegrini (2012)[84]	N/A	326	1488	Uruguay	Interviewed 64-item FFQ for previous 5 years	Tertiles of fish intake (continuous servings per year, not defined)	↔ PrCa risk OR 1.34 (0.95-1.89) *P* = .09
Kristal et al (2002)[66]	Seattle-Puget Sound Surveillance Epidemiology and End Results Registry	605	592	Seattle, WA	Self-administered FFQ for previous 3-5 years	>0.24 g/d EPA + DHA intake (food and supplements)	↔ local PrCa risk AOR 1.05 (0.68-1.63) *P* = .51 ↔ regional/distant PrCa risk AOR 0.84 (0.44-1.58) *P* = .81
Joshi et al (2012)[63]	California Collaborative Prostate Cancer Study	717 localized, 1140 advanced	1096	California	Interviewed FFQ for previous 12-month intake	Tertiles fish intake White fish: >12.41-167 g/1000 kcal/d	↔ PrCa risk T3 intake tuna, dark fish or deep-fried fish ↑ risk advanced PrCa white fish AOR 1.3 (1.0-1.7) *P*trend = .014
Raimondi et al (2010)[58]	N/A	197	197	Canada	FFQ for 1 year prior to diagnosis	Finfish/shellfish intake >30.4 g/d	↓ PrCa risk OR 0.54 (0.30-0.97) *P* = .05
Fradet et al (2009)[59]	N/A	466	478	USA	FFQ reflecting the period before diagnosis	EPA intake 0.167 g/d DHA intake 0.368 g/d	↓ PrCa risk EPA AOR 0.35 (0.24-0.52) *P* < .0001; DHA AOR 0.36 (0.25-0.53) *P* < .0001
						>1 serving per week dark fish	↓ PrCa risk AOR 0.43 (0.29-0.63) *P*trend < .0001
						>1 serving per week white fish	↓ PrCa risk AOR 0.66 (0.45-0.96) *P*trend = .32
						>1 serving per week shellfish	↓ PrCa risk AOR 0.51 (0.35-0.74) *P*trend < .0001
						>1 serving per week tuna	↓ PrCa risk AOR 0.75 (0.51-1.09) *P* = .04
						>1 serving per week fried fish	↓ PrCa risk AOR 0.56 (0.37-0.86) *P* = .03
Assessing blood levels and dietary intake of fatty acids							
Norrish et al (1999)[22]	Auckland Prostate Study	317	480	Auckland, New Zealand	Self-administered 107-item FFQ and RBC EPA and DHA	Quartiles EPA and DHA intake (not defined) RBC EPA >0.83 mol% and RBC DHA >1.70 mol%	↔ PrCa risk EPA mvRR 0.96 (0.63-1.48) DHA mvRR 1.10 (0.71-1.70) ↓ PrCa risk EPA RR 0.59 (0.37-0.95) DHA RR 0.62 (0.39-0.98)

Abbreviations: PrCa, prostate cancer; mvRR, multivariate relative risk; mvHR, multivariate hazard ratio; AOR, adjusted odds ratio; FFQ, Food Frequency Questionnaire; ×/wk, times per week; f/u follow-up; BI, baseline; ↓, decrease; ↑, increase; ↔, no change; FA, fatty acids; PPL, plasma phospholipids; RBC, red blood cell; n-3, omega-3; PUFA, polyunsaturated fatty acids; sICAM-1, soluble intercellular adhesion molecule-1; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid.

Table 6. Nested Case-Control Studies of Fish-Derived Omega-3 Fatty Acids and Prostate Cancer Incidence.

Reference	Cohort/Study Name	Cases n	Controls n	Geographic Area	Exposure Assessment	Highest Group (Quartile, Quintile, etc)	Effect of Exposure on Outcome (Highest vs Lowest Exposure)
Assessing blood levels of fatty acids							
Dahm et al (2012)[65]	European Prospective Investigation into Cancer and Nutrition (EPIC) cohort	962	1061	10 European countries	Plasma FAs at baseline	Quintiles of plasma marine n-3 PUFA (not defined)	↑ risk of PrCa based on treelet transform analysis OR 1.36 (0.99, 1.86) *P*trend = .041
Crowe et al (2008)[40]	European Prospective Investigation into Cancer and Nutrition (EPIC)	926	926	10 European countries	Plasma PPL FAs	EPA 1.95-9.49 mol%	↔ risk of total PrCa mvRR 1.31 (0.96-1.81) *P* = .09 ↑ risk of high-grade PrCa mvRR 2.00 (1.07-3.76) *P*trend = 0.031 ↔ risk of localized, advanced or low-grade PrCa
						DHA 5.34-10.37 mol%	↔ risk of total PrCa DHA mvRR 1.39 (1.02-1.90) *P* = .158 ↔ risk of localized, advanced, high-grade or low-grade PrCa
Brasky et al (2011)[38]	Prostate Cancer Prevention Trial	1658	1803	USA	Serum PPL FA at baseline	EPA >0.74%	↔ risk of low-grade or high-grade PrCa
						DHA >3.30%	↑ risk high-grade PrCa OR 2.50 (1.34, 4.65) *P* = .04 ↔ risk of low-grade PrCa
						EPA + DHA >4.02%	↔ risk of low-grade ↔ risk of high-grade PrCa AOR 1.99 (1.08-3.68) *P* = .08
Park (2009)[85]	The Multiethnic Cohort Study	376	729	USA	RBC FA at baseline	EPA >0.77% DHA >8.00%	↔ risk PrCa
Chavarro et al (2008)[41]	Physician's Health Study	476	476	USA	Whole blood FAs	EPA >2.36%	↓ risk of localized PrCa mvRR 0.57 (0.36-0.92) *P* = .02 ↔ risk of advanced, aggressive or nonaggressive PrCa
						DHA >3.37%	↓ risk of localized PrCa mvRR 0.60 (0.39-0.93) *P* = .07 ↔ risk of advanced, aggressive or nonaggressive PrCa
Harvei et al (1997)[67]	N/A	141	141	Norway	Serum PPL FAs	EPA 2.00% DHA 5.67%	↔ risk of PrCa EPA OR 1.2 (0.6-1.2) *P* = .1; DHA OR 1.0 (0.5-1.8) *P* = .08
Assessing dietary intake of fatty acids							
Touvier (2012)[86]	SUVIMAX (Supplementation en Vitamines et Mineraux AntioXydants) Cohort Study	129	760	France	24-hour dietary records every 2 mo for first 2 years of study; baseline plasma sICAM-1	1.2 g/d n-3 fatty acid intake in women, 1.6 g/d in men	Relation between sICAM-1and PrCa modulated by n-3 PUFA intake; sICAM-1 associated with ↑ risk PrCa in patients with n-3 intakes below the median OR 6.1; (1.1-34.5) *P*trend = .03; no association in patients with intakes above median OR 0.3 (0.1-1.6) *P*trend = .2
Torfadottir et al (2013)[36]	AGES-Reykjavik Cohort Study	343	1914	Iceland	FFQ assessing early, mid- and late-life fish intake	>4 servings total fish/wk	↔ PrCa risk with intake early- and midlife AOR 0.87 (95% CI: 0.66, 1.13), 1.05 (95% CI: 0.71, 1.57)
						Once a week or more intake of salted or smoked fish	↑ risk advanced PrCa intake early life OR 1.98 (95% CI: 1.08, 3.62); ↔ risk with intake in midlife ↔ risk of total and localized PrCa with intake in early life, midlife
						Fish oil use daily	↔ risk of total, localized, or advanced PrCa with supplementation in early life or midlife
Assessing blood levels and dietary intake of fatty acids							
Gann (1994)[87]	Physician's Health Study	120	120	USA	Plasma FAs and FFQ at baseline	Quartiles of plasma FAs (not defined)	↔ risk of PrCa EPA RR 0.87 (0.41-1.82) *P* = .81

Abbreviations: PrCa, prostate cancer; mvRR, multivariate relative risk; mvHR, multivariate hazard ratio; AOR, adjusted odds ratio; FFQ, Food Frequency Questionnaire; ×/wk, times per week; f/u follow-up; BI, baseline; ↓, decrease; ↑, increase; ↔, no change; FA, fatty acids; PPL, plasma phospholipids; RBC, red blood cell; n-3, omega-3; PUFA, polyunsaturated fatty acids; sICAM-1, soluble intercellular adhesion molecule-1; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid.

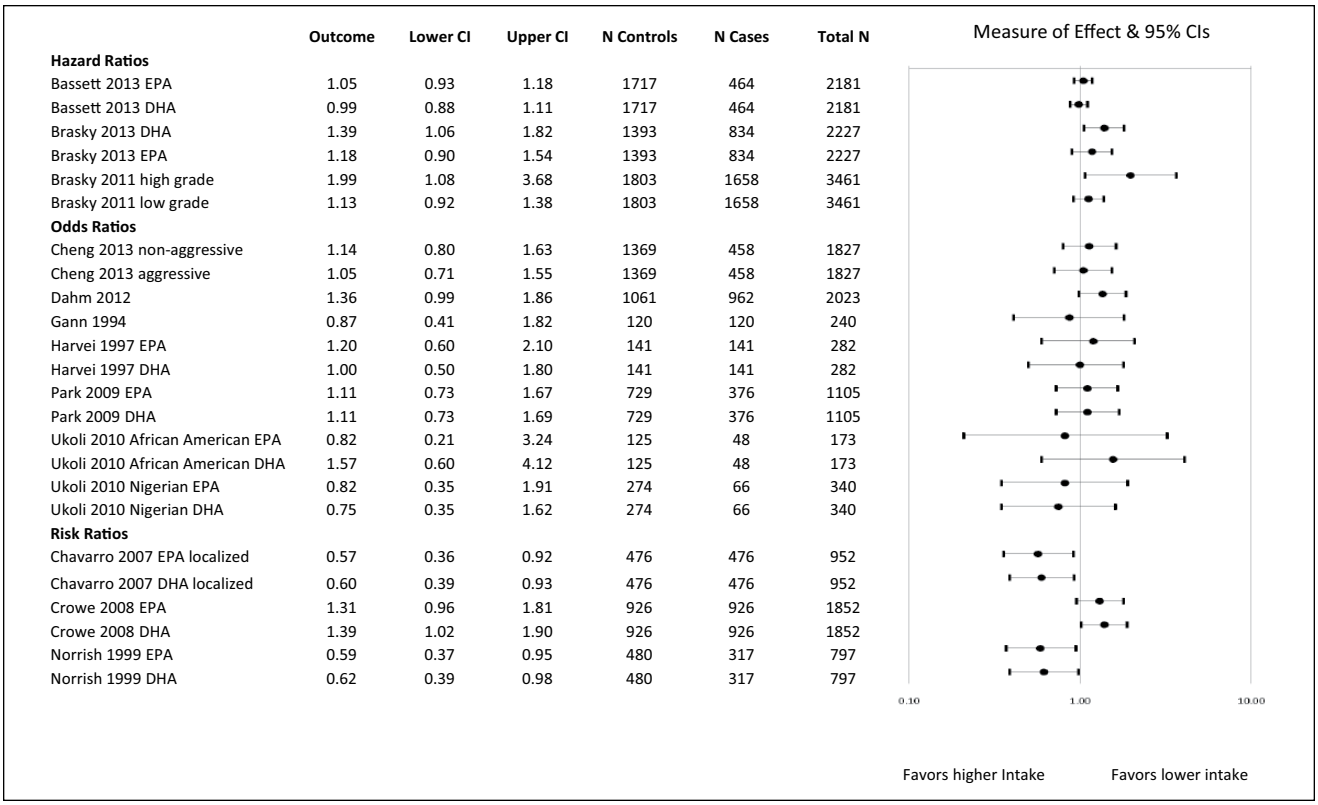


Figure 4. Risk of prostate cancer (PrCa) incidence with fish-derived omega-3 fatty acid intake: Case-cohort, case-control, and nested case-control studies using blood assessment of fatty acids. When the effect of total fish-derived omega-3 fatty acid intake on PrCa risk was not available, sub-analyses reporting on individual fatty acids or different stages of cancer are reported.

for intake of other fish) and no effect from higher intake of tuna, dark fish, or deep fried fish.[63] Another study that found an association with increased risk reported mixed results including an increased risk of advanced PrCa with higher intake of salted or smoked fish in early life, a lower risk of localized PrCa with intake later in life and no effect on other stages of PrCa and other intake time points.[36]

No case-cohort, case-control, or nested case-control studies reported on the risk of death.

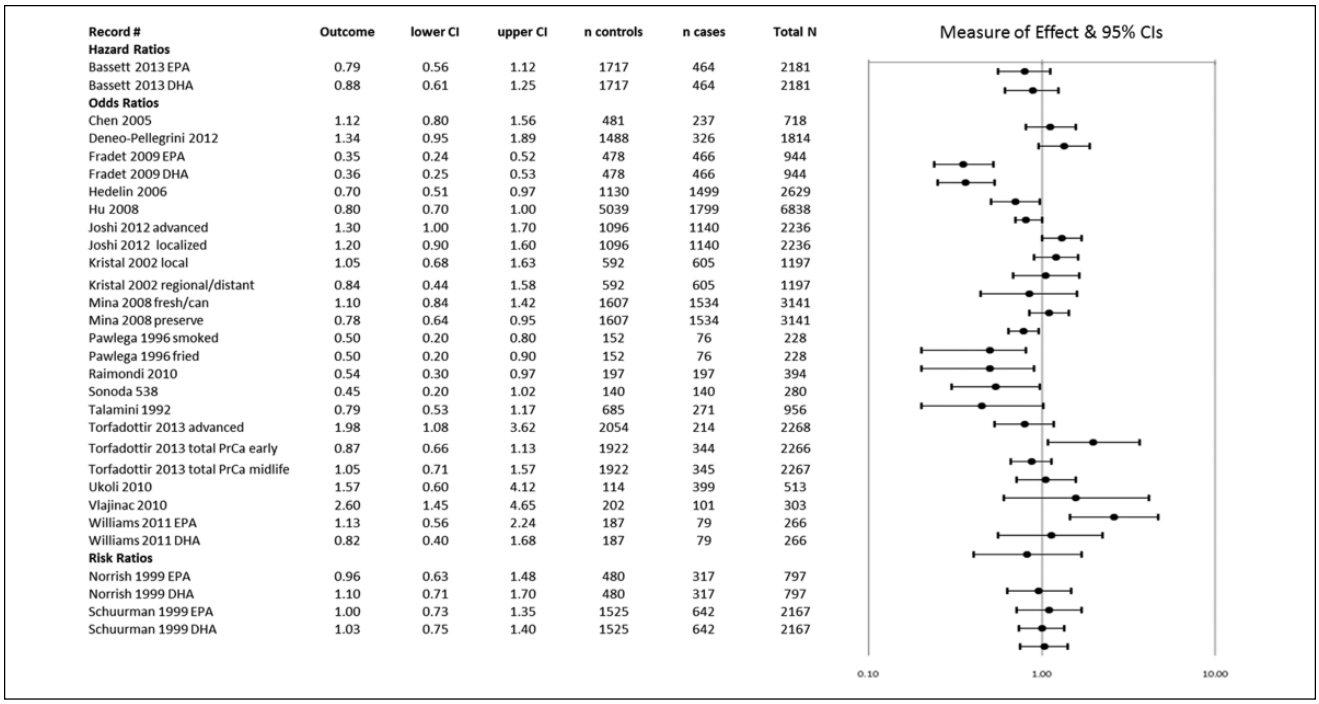
One case-control study assessed supplemental fish oil intake in addition to dietary fish intake; however, the intake amounts were combined in analysis to reflect overall fish-derived omega-3 fatty acid intake.[66] One nested case-control study assessed supplemental fish oil intake and found that daily use in early or midlife was not associated with and PrCa risk.[36]

When the observational results were organized by the type of fish-derived fatty acid analyzed (EPA and DHA), no association was observed (Figures 6 and 7).

Adverse Events and Interactions. In the RCTs and non-RCT, adverse events ranged from none to mild. In 1 study, 2 of 32 subjects experienced nausea and withdrew.[28] One study reported increased flatulence (5 subjects compared with 1 in the placebo group), self-limiting diarrhea (2 participants compared with 1 in the placebo group), and eructation (1 participant).[29] Two studies stated that no adverse events were reported.[31,32] No studies reported a statistically significant difference in adverse reaction rates between fish oil and control/placebo arm.

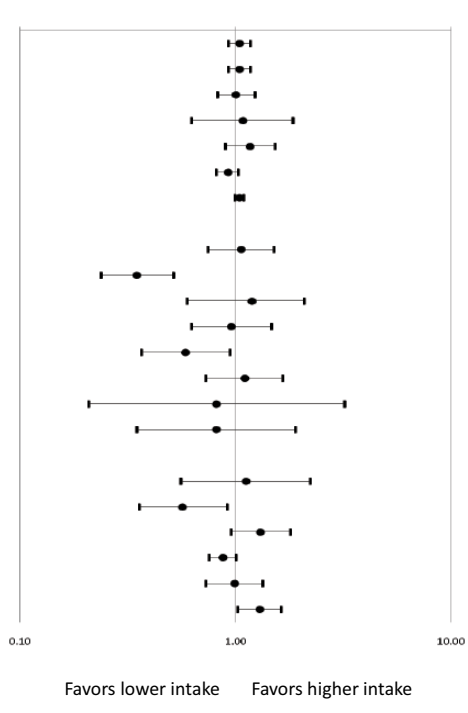
Among the studies that used fish oil supplement interventions in patients with PrCa, no interactions with conventional care were reported; however, the studies excluded many participants receiving conventional cancer therapies. Of the 3 RCTs and 1 non-RCT, 3 excluded men receiving antihormonal therapies, 2 excluded men receiving 5-alpha-reductase inhibitors, and 3 excluded men taking anti-inflammatory medication. None of the studies included men receiving chemotherapy or radiation; 2 studies included men who were untreated,[31,32] 1 included men postprostatectomy,[28] and 1 preprostatectomy.[29] No clinical studies specifically reported an active assessment of interactions with other therapies, surgical procedures, or medications.

Risk of Bias. Among the RCTs, all studies had a high risk of bias when evaluated with the Cochrane Risk of Bias Assessment; the results are displayed in Figure 8. Risk was identified in most studies due to incomplete outcome data and in



Record #	Outcome	lower CI	upper CI	n controls	n cases	Total N
Hazard Ratios						
Bassett 2013 EPA	0.79	0.56	1.12	1717	464	2181
Bassett 2013 DHA	0.88	0.61	1.25	1717	464	2181
Odds Ratios						
Chen 2005	1.12	0.80	1.56	481	237	718
Deneo-Pellegrini 2012	1.34	0.95	1.89	1488	326	1814
Fradet 2009 EPA	0.35	0.24	0.52	478	466	944
Fradet 2009 DHA	0.36	0.25	0.53	478	466	944
Hedelin 2006	0.70	0.51	0.97	1130	1499	2629
Hu 2008	0.80	0.70	1.00	5039	1799	6838
Joshi 2012 advanced	1.30	1.00	1.70	1096	1140	2236
Joshi 2012 localized	1.20	0.90	1.60	1096	1140	2236
Kristal 2002 local	1.05	0.68	1.63	592	605	1197
Kristal 2002 regional/distant	0.84	0.44	1.58	592	605	1197
Mina 2008 fresh/can	1.10	0.84	1.42	1607	1534	3141
Mina 2008 preserve	0.78	0.64	0.95	1607	1534	3141
Pawlega 1996 smoked	0.50	0.20	0.80	152	76	228
Pawlega 1996 fried	0.50	0.20	0.90	152	76	228
Raimondi 2010	0.54	0.30	0.97	197	197	394
Sonoda 538	0.45	0.20	1.02	140	140	280
Talamini 1992	0.79	0.53	1.17	685	271	956
Torfadottir 2013 advanced	1.98	1.08	3.62	2054	214	2268
Torfadottir 2013 total PrCa early	0.87	0.66	1.13	1922	344	2266
Torfadottir 2013 total PrCa midlife	1.05	0.71	1.57	1922	345	2267
Ukoli 2010	1.57	0.60	4.12	114	399	513
Vlajinac 2010	2.60	1.45	4.65	202	101	303
Williams 2011 EPA	1.13	0.56	2.24	187	79	266
Williams 2011 DHA	0.82	0.40	1.68	187	79	266
Risk Ratios						
Norrish 1999 EPA	0.96	0.63	1.48	480	317	797
Norrish 1999 DHA	1.10	0.71	1.70	480	317	797
Schuurman 1999 EPA	1.00	0.73	1.35	1525	642	2167
Schuurman 1999 DHA	1.03	0.75	1.40	1525	642	2167

Figure 5. Risk of prostate cancer (PrCa) incidence with fish-derived omega-3 fatty acid intake: Case-cohort, case-control, and nested case-control studies using Food Frequency Questionnaire (FFQ) assessment of fatty acid exposure. When the effect of total fish-derived omega-3 fatty acid intake on PrCa risk was not available, subanalyses reporting on individual fatty acids, different stages of cancer, and different time points of fish exposure are reported.



	Outcome	Lower CI	Upper CI	N Total	N Cases	N Total
Hazard Ratios						
Bassett 2013 FFQ	1.05	0.93	1.18	1717	464	2181
Bassett 2013 serum FA	1.05	0.93	1.18	1717	464	2181
Brasky 2011 low grade	1.01	0.83	1.24	1803	1658	3461
Brasky 2011 high grade	1.09	0.63	1.86	1803	1658	3461
Brasky 2013	1.18	0.90	1.54	1393	834	2227
Pelser 2013 adv	0.93	0.82	1.04	285338	2930	288268
Pelser 2013 nonadv	1.05	1.00	1.10	269334	18934	288268
Odds Ratios						
Cheng 2013	1.07	0.75	1.52	1369	458	1827
Fradet 2009	0.35	0.24	0.52	478	466	944
Harvei 1997	1.20	0.60	2.10	141	141	282
Norrish 1999 FFQ	0.96	0.63	1.48	480	317	797
Norrish 1999 RBC FA	0.59	0.37	0.95	480	317	797
Park 2009	1.11	0.73	1.67	729	376	1105
Ukoli 2010 African American	0.82	0.21	3.24	125	48	173
Ukoli 2010 Nigerian	0.82	0.35	1.91	274	66	340
Risk Ratios						
Williams 2011	1.13	0.56	2.24	187	79	266
Chavarro 2007	0.57	0.36	0.92	476	476	952
Crowe 2008	1.31	0.96	1.81	926	926	1852
Leitzmann 2004	0.88	0.76	1.01	44901	2965	47866
Schuurman 1999	1.00	0.73	1.35	1525	642	2167
Wallstorm 2007	1.30	1.03	1.64	10564	817	11381

Figure 6. Risk of prostate cancer (PrCa) incidence with eicosapentaenoic acid (EPA) intake: Observational data. When the effect of total fish-derived omega-3 fatty acid intake on PrCa risk was not available, subanalyses reporting on individual fatty acids or different stages of cancer are reported.

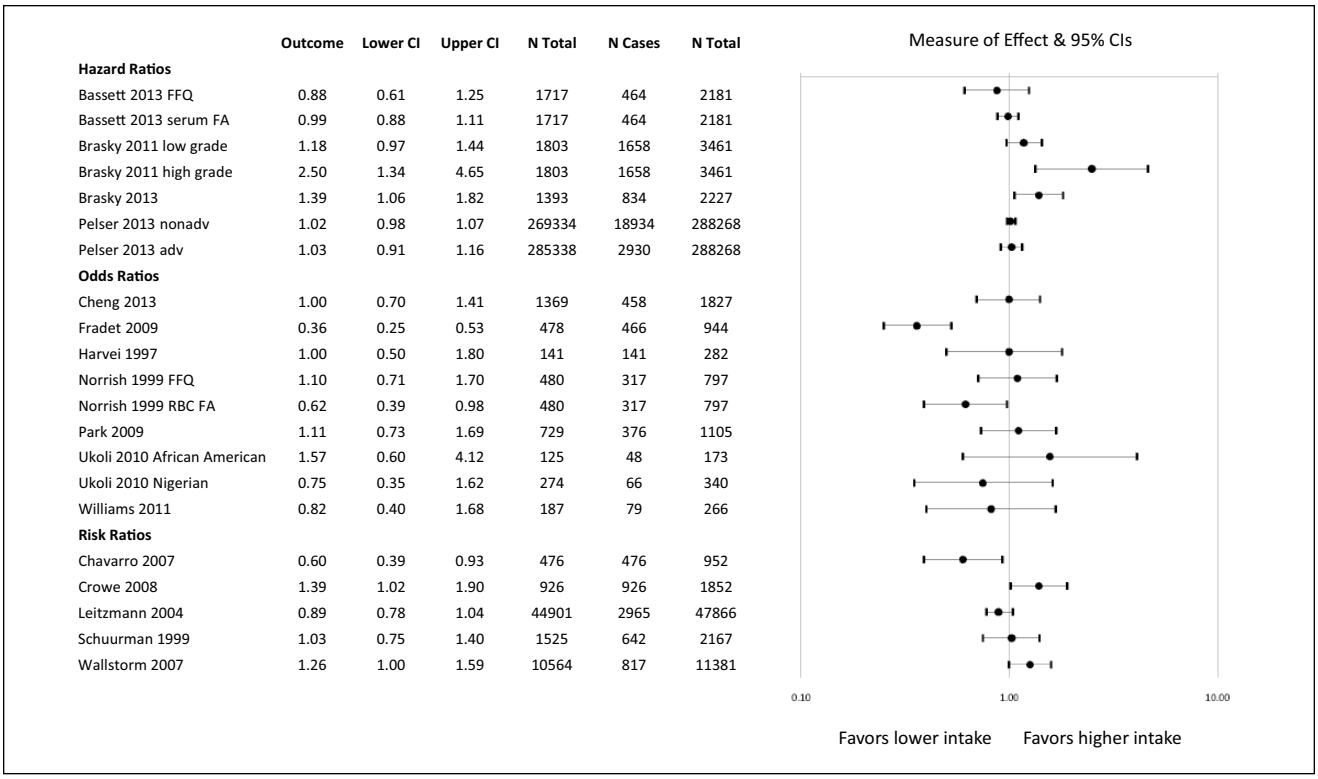


Figure 7. Risk of prostate cancer (PrCa) incidence with docosahexaenoic acid (DHA) intake: Observational data. When the effect of total fish-derived omega-3 fatty acid intake on PrCa risk was not available, sub-analyses reporting on individual fatty acids or different stages of cancer are reported.

some studies due to lack of blinding for participants and in outcome assessment. Allocation concealment was unclear in all studies. Among the 3 RCTs, 1 was industry funded,[28] 1 was non–industry funded,[29] and 1 was funded by a combination.[31] The 1 nonrandomized clinical trial did not use blinding, had no loss to follow-up; and a priori sample size estimation and funding source were unclear.[32]

Among the observational studies, the cohort studies, case-control studies and case-cohort studies had an average score of 7.06, 7.27, and 8.33 out of 9, respectively, on the Newcastle-Ottawa Quality Assessment Scale. Two cohort studies were not assessed because full text publication in English was not available.[42,44] The results are displayed in Figures 9, 10, and 11. The most notable deficiency in both the cohort and case-control studies was for the ascertainment of fish-derived omega-3 fatty acid exposure as most studies relied on written, self-report of dietary information rather than a structured interview. Additionally, many of the case-control studies failed to report the difference in nonresponse rate between cases and controls. Among the observational studies, 40 were funded by nonindustry sources, 2 by a combination of industry and nonindustry sources,[34,36] and 8 were unclear in their reporting of funding.[43,47,56-58,67-69]

Discussion

Summary of Findings

The interventional studies of fish-derived omega-3 in patients with PrCa showed no impact on PSA levels; however, some studies showed a decrease in inflammatory markers. A small number of mild adverse events were reported and interactions with other interventions were not assessed. Cohort, case-cohort and case-control studies assessing the risk of PrCa incidence were equivocal. Cohort studies assessing the risk of PrCa mortality suggested an association between higher intake and decreased risk. The results of this review are consistent with other systematic reviews conducted,[70,71] which also assessed prevention and secondary PrCa outcomes using diet and supplement exposure and found no association.

Study Weaknesses: Method of Exposure Ascertainment in Observational Studies

While all of the cohort studies assessed patient-reported fish-derived omega-3 fatty acid intake to ascertain exposure, case-control and nested case-control studies utilized either patient questionnaires or blood levels to assess

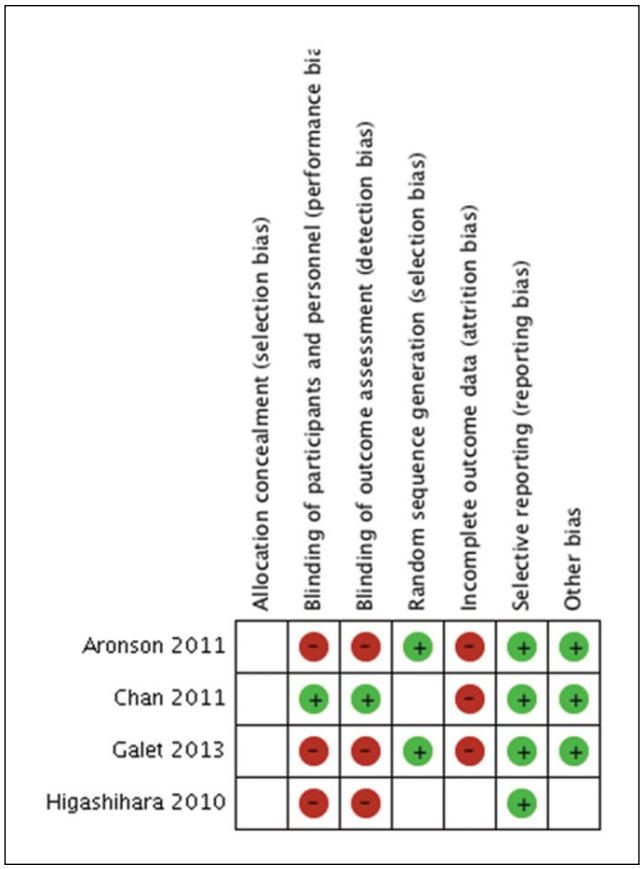


Figure 8. Cochrane Risk of Bias Assessment of randomized controlled trials (RCTs). (+), low risk of bias; (−), high risk of bias; neither symbol, unclear risk of bias.

fish-derived omega-3 fatty acid exposure; however, both have limitations. The method of assessing fish-derived omega-3 fatty acid exposure may be of importance as more of the studies utilizing blood levels reported an association with increased risk of PrCa while more of the studies assessing self-reported intake reported an association with deceased risk of PrCa. A recent study compared the different methods of fish intake assessment.[72] They followed a group of men with low-risk PrCa undergoing active surveillance to first repeat biopsy and assessed relationships between the risk of progression and the different methods of fatty acid assessment—dietary recall, RBC fatty acids, and prostate tissue fatty acids. While dietary intake and RBC fatty acids were not correlated with risk of progression, men with the highest tertile of prostate EPA had a significantly lower risk of progression (OR = 0.08, 95% CI 0.01-0.72, $P = .02$).

Blood assessment is limited by the challenge of differentiating endogenously produced fats from those consumed and the impact of individually varying rates of metabolism and deposition in tissues as a result of genetic, dietary and lifestyle differences.[73] Additionally an individual fatty acid is reported as a percentage of total fatty acids, not as an absolute amount; as a result, larger intake of one fatty acid could affect the relative proportion of others. Lastly, disease can affect fatty acid levels; for example, tumors selectively take up high amounts of polyunsaturated fatty acids.[73] Among the studies included in this review that used blood samples, 9 of 12 assessed plasma or serum fatty acids, 2 assessed RBC fatty acids and 1 assessed whole blood. Plasma fatty acids are known to reflect short-term or recent fat intake while RBCs reflect the previous 3 weeks' to 3 months' intake due to their longer life span.[74] Considering the length of time required for the pathogenesis of cancerous lesions, these fatty acid evaluations that reflect relatively recent intake may be of limited utility in assessing a role in causation, particularly if the participant has made changes to their diet over time.

Diet recall also presents challenges, including intentionally or unintentionally inaccurate recall and low reproducibility. Studies assessing the reproducibility of FFQs for polyunsaturated fatty acids have found a Spearman correlation coefficient from 0.38 to 0.59.[75] With cancer known to develop over a long period of time, some of the shorter times between observation of exposure and outcome of interest may neither be sufficient to allow for detection, progression, or substantive change, nor represent the time when carcinogenesis or early cancer development occurred. Conversely, when studies asked participants to recall dietary patterns from 10 years ago, there could be concern about the patients' ability to do so accurately.

Possible Mechanisms of Protective Effect

There have been a number of proposed mechanisms by which fish-derived omega-3 fatty acids may influence PrCa risk or progression, largely related to their effect on decreasing inflammation through inhibition of the cyclooxygenase enzymes[76] and affecting the immune system. Inflammation is suspected to trigger PrCa progression[77] and the use of nonsteroidal anti-inflammatory drugs (NSAIDS) results in a decreased risk of PrCa.[61] In vitro studies assessing the impact of fish oil on PrCa cells demonstrate increased cancer cell death,[12] enhanced cytotoxic effects of docetaxel,[13] prolongation of the androgen-dependent state,[14] and inhibition of cell adhesion, invasion and migration, which effect metastasis.[15,16] A mouse study comparing diets based on fish, olive, corn, or animal fat showed slowed tumor growth and increased survival in the fish oil group.[17]

Alternatively, another factor in the fish may be exerting an anticancer effect. Dietary fish is a source of vitamin D[78] and while results are varied, vitamin D is suspected to have a possible protective effect in prostate cancer.[79] None of the studies reviewed assessed vitamin D levels; however, one study acknowledged that the protective effect of fish oil supplementation may have been related to the vitamin D

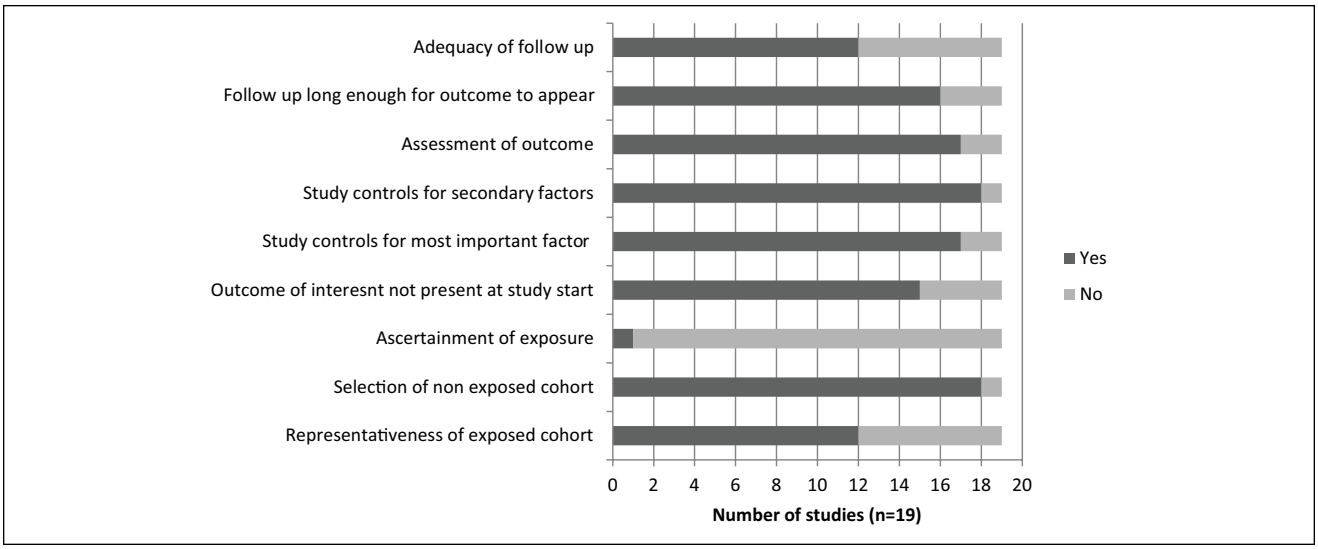


Figure 9. Newcastle-Ottawa Quality Assessment Scale: Cohort studies.

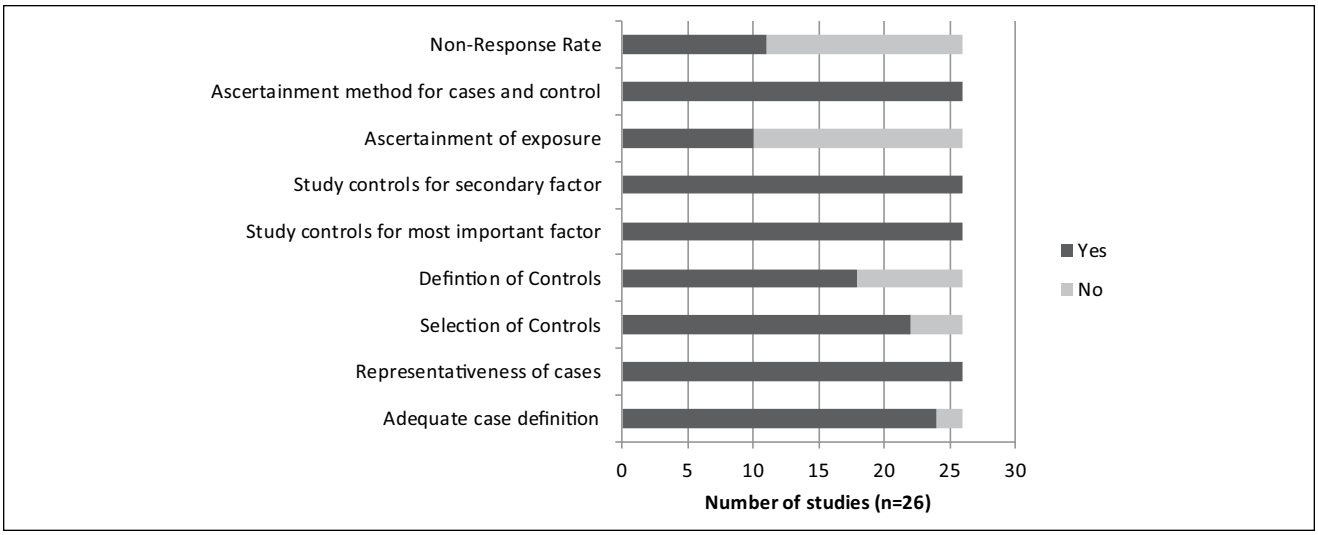


Figure 10. Newcastle-Ottawa Quality Assessment Scale: Case-control studies.

content found in fish liver oil, the most common form of fish oil supplementation used in the study population.[36]

Possible Mechanisms of Harmful Effect

Some of the studies reviewed found associations between higher fish-derived omega-3 fatty acid exposure and PrCa incidence risk. No biological mechanism has been proposed to explain these results. The studies suggesting harm were more likely to be retrospective studies than prospective studies and many showed a combination of harmful, protective or null effect, resulting in unclear conclusions. Although they were of short duration, the intervention trials did not produce results suggesting a risk in the form of side effects, or negative effects on clinical outcomes such as laboratory markers or mortality.

One study suggested that the omega-3:omega-6 ratio might be of more importance than the absolute amount of marine omega-3 intake because of their competitive metabolism and antagonistic effects on inflammation.[61] The study conducted by Joshi et al[63] explored the relationship between different types of fish, different methods of preparation, different levels of "done-ness" (ie, preconsumption cooking and/or preparation) and the risk of PrCa. Fish that was pan-fried or cooked to "well done" was associated with increased risk while fish cooked "just until done," "well done at low

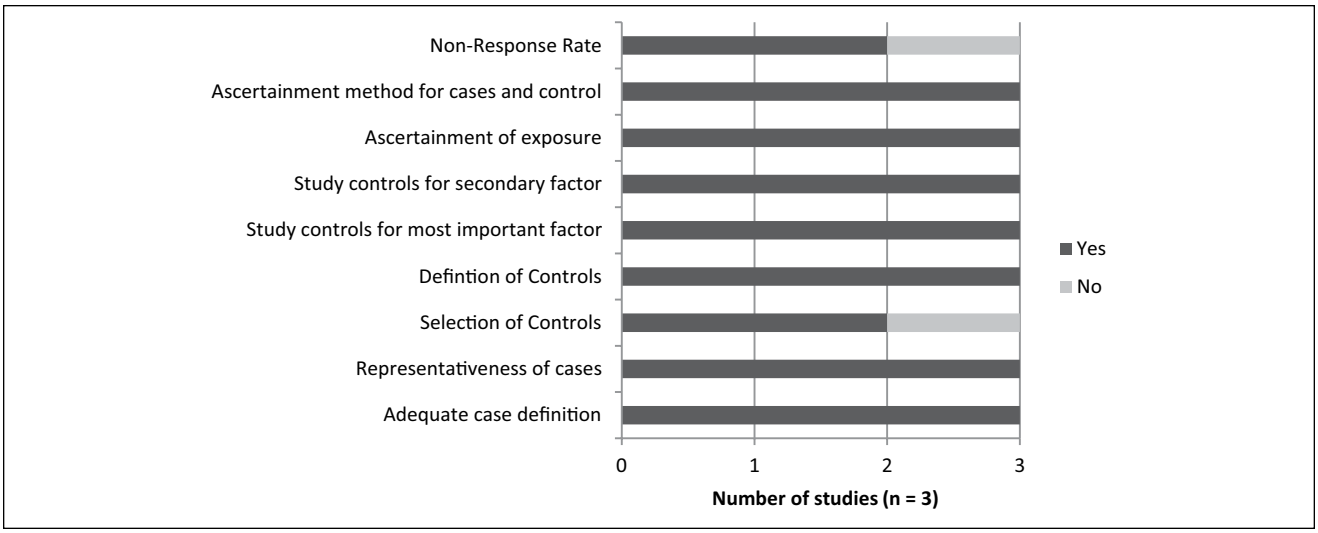


Figure 11. Newcastle-Ottawa Quality Assessment Scale: Case-cohort studies.

temperatures," and "just done at high temperatures" was not. The authors concluded that mutagenic heterocyclic amines produced in cooking might be responsible for the association.

Other studies hypothesized that environmental toxins, such as polychlorinated biphenyls found in the fish that was ingested,[43] or involved in processing and packaging,[62] could be the biologically active constituent responsible for the association with cancer rather than the fatty acids EPA + DHA.

While not part of this systematic review, a brief search of preclinical data yielded only 1 study showing procancer effects of EPA at low concentrations in cancer cell lines. The remaining 50 in vitro/in vivo studies reported anticancer effects or mechanisms of omega-3 fatty acids (Appendix B). Unlike the observational studies that posed very large challenges in assessing exposure, the cell culture and animal studies involved doses of fish oil exposure that were was precisely known.

Alternatively, the relationship may be related to a behavioral factor rather than a biological one. PrCa risk is increased with increasing education, which may be associated with more health conscious behaviors such as consuming dietary fish or fish oil supplements.[80]

Systematic Review Strengths and Limitations

Strengths of our review include a comprehensive search including all interventional and observational studies conducted in humans. Our methodology, including duplication of screening and data extraction demonstrates reliability of the synthesis.

One significant limitation of this review relates to primary research available and specifically the lack of well designed, long duration studies examining the effects of fish oil interventions in patients with or without PrCa. Of the 4 interventional studies reported on, 3 studies were 3 months or shorter in duration, which may not be an adequate length of time to observe a response to treatment, progression, recurrence of PrCa or to monitor long-term adverse events. Because of the relatively small number of studies assessing the role of fish oil in patients with PrCa, the majority of the evidence included in this review assessed primary prevention of PrCa. While this information may be useful in understanding a potential anticancer or procancer effect of these constituents, it is a significant limitation in answering the original question of whether or not fish oil supplementation is indicated in patients with PrCa. Because the majority of the studies were observational, the results provide limited information on causality and may reflect correlations or other associations. Additionally, the methods used to assess exposure possessed limitations. Although we included a large number of studies, it was not possible to pool the data due to heterogeneity.

Conclusions

Taken together, there are inadequate data to determine if fish-derived omega-3 fatty acids are associated with PrCa incidence and progression and how to advise PrCa patients who are considering fish oil supplementation. Preliminary research suggests that an association between higher omega-3 intake and decrease PrCa mortality may be present but more research is needed. Because of the challenges related to assessing exposure, more intervention trials or observational studies with precisely measured exposure and longer duration are needed to assess the impact of supplemental or dietary fish-derived omega-3 fatty acid intake on PrCa incidence, treatment and progression.

Appendix A

Prostate Cancer—Omega 3

Final Search Strategy
2014 Jul 21

OVID Searches

Database: AMED (Allied and Complementary Medicine) <1985 to July 2014>, Embase Classic+Embase <1947 to 2014 July 18>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present> Search Strategy:

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1 exp Prostatic Neoplasms/ (253131)
2 ((prostate or prostatic) adj3 (cancer* or carcinoid* or carcinoma* or carcinogen* or adenocarcinoma* or adeno-carcinoma* or malignan* or neoplasia* or neoplasm* or sarcoma* or tumour* or tumor*)).tw. (230129)
3 ((prostate or prostatic) adj3 (anticancer* or anti-cancer* or anticarcinogen* or anti-carcinogen* or antineoplas* or anti-neoplas* or chemoprevent* or chemo-prevent* or (tumo?r adj2 suppress*))).tw. (2285)
4 Prostate/de (3838)
5 Prostatic Hyperplasia/ (47434)
6 ((prostate or prostatic) adj3 (hyperplasia* or adenoma* or hypertroph* or enlarg*)).tw. (40106)
7 BPH.tw. (19805)
8 Prostate-Specific Antigen/ (55668)
9 (PSA or prostate-specific antigen* or prostatic-specific antigen* or gamma-seminoprotein* or (hK3 adj1 Kallikrein) or semenogelase or seminin).tw. (76299)
10 or/1-9 (349314)
11 Fatty Acids, Omega-3/ (25712)
12 Eicosapentaenoic Acid/ (15147)
13 (eicosapentanoic acid* or icosapentaenoic acid* or icosapentaenoate or omega-3-eicosapentaenoic acid* or timnodonic acid* or eicosapen).tw. (600)
14 ("5,8,11,14,17-Eicosapentaenoic Acid" or "5,8,11,14,17-Icosapentaenoic Acid").tw. (143)
15 EPA.tw. (24393)
16 Eicosapentaenoic Acid.rn. (4358)
17 exp Docosahexaenoic Acids/ (18855)
18 (docosahexaenoic acid* or docosahexaenoate or dhasco).tw. (18092)
19 dha.tw. (20493)
20 25167-62-8.rn. (17617)
21 ("omega 3" or omega3 or n-3 fatty acid* or n3 fatty acid* or n-3 polyunsaturated fatty acid* or n-3 poly-unsaturated fatty acid* or n3 polyunsaturated fatty acid* or n3 poly-unsaturated fatty acid* or n-3 PUFA or n3 PUFA or PUFAs).tw. (35392)
22 (Maxepa or Omacor).tw. (998)
23 or/11-22 (80037)
24 10 and 23 (816)
25 exp Fishes/ (309824)
26 exp Food/ (1803802)
27 exp Diet/ (439211)
28 25 and (26 or 27) (34591)
29 (fish$2 or fishoil* or shellfish$2 or shell fish$2 or seafood* or sea food* or marine*).tw. (403998)
30 28 or 29 (415408)
31 10 and 30 (2226)
32 24 or 31 (2842)
33 exp Animals/ not (exp Animals/ and Humans/) (8758181)
34 32 not 33 (2574)
35 (comment or editorial or interview or letter or news).pt. (2839640)

36 34 not 35 (2521)
37 36 use prmz (860)
38 exp prostate cancer/ (228398)
39 ((prostate or prostatic) adj3 (cancer* or carcinoid* or carcinoma* or carcinogen* or adenocarcinoma* or adeno-carcinoma* or malignan* or neoplasia* or neoplasm* or sarcoma* or tumour* or tumor*)).tw. (230129)
40 ((prostate or prostatic) adj3 (anticancer* or anti-cancer* or anticarcinogen* or anti-carcinogen* or antineoplas* or anti-neoplas* or chemoprevent* or chemo-prevent* or (tumo?r adj2 suppress*))).tw. (2285)
41 prostate hypertrophy/ (29272)
42 ((prostate or prostatic) adj3 (hyperplasia* or adenoma* or hypertroph* or enlarg*)).tw. (40106)
43 BPH.tw. (19805)
44 prostate specific antigen/ (55668)
45 (PSA or prostate-specific antigen* or prostatic-specific antigen* or gamma-seminoprotein* or (hK3 adj1 Kallikrein) or semenogelase or seminin).tw. (76299)
46 or/38-45 (337349)
47 omega 3 fatty acid/ (28576)
48 icosapentaenoic acid/ (10789)
49 (eicosapentanoic acid* or icosapentaenoic acid* or icosapentaenoate or omega-3-eicosapentaenoic acid* or timnodonic acid* or eicosapen).tw. (600)
50 ("5,8,11,14,17-Eicosapentaenoic Acid" or "5,8,11,14,17-Icosapentaenoic Acid").tw. (143)
51 EPA.tw. (24393)
52 1553-41-9.rn. (164)
53 icosapentaenoic acid.rn. (9979)
54 docosahexaenoic acid/ (13096)
55 (docosahexaenoic acid* or docosahexaenoate or dhasco).tw. (18092)
56 dha.tw. (20493)
57 25167-62-8.rn. (17617)
58 docosahexaenoic acid.rn. (11891)
59 ("omega 3" or omega3 or n-3 fatty acid* or n3 fatty acid* or n-3 polyunsaturated fatty acid* or n-3 poly-unsaturated fatty acid* or n3 polyunsaturated fatty acid* or n3 poly-unsaturated fatty acid* or n-3 PUFA or n3 PUFA or PUFAs).tw. (35392)
60 (Maxepa or Omacor).tw. (998)
61 or/47-60 (80408)
62 46 and 61 (839)
63 exp fish/ (173462)
64 exp food/ (1803802)
65 exp diet/ (439211)
66 63 and (64 or 65) (19916)
67 (fish$2 or fishoil* or shellfish$2 or shell fish$2 or seafood* or sea food* or marine*).tw. (403998)
68 66 or 67 (410094)
69 46 and 68 (2203)
70 62 or 69 (2836)
71 exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (37835447)
72 exp humans/ or exp human experimentation/ or exp human experiment/ (28781117)
73 71 not 72 (9055973)
74 70 not 73 (2577)
75 (editorial or letter).pt. (2524137)
76 74 not 75 (2527)
77 76 use emczd (1648)
78 prostatic neoplasms/ (119512)
79 ((prostate or prostatic) adj3 (cancer* or carcinoid* or carcinoma* or carcinogen* or adenocarcinoma* or adenocarcinoma* or malignan* or neoplasia* or neoplasm* or sarcoma* or tumour* or tumor*)).tw. (230129)
80 ((prostate or prostatic) adj3 (anticancer* or anti-cancer* or anticarcinogen* or anti-carcinogen* or antineoplas* or anti-neoplas* or chemoprevent* or chemo-prevent* or (tumo?r adj2 suppress*))).tw. (2285)

81 exp prostatic hypertrophy/ (47487)
82 ((prostate or prostatic) adj3 (hyperplasia* or adenoma* or hypertroph* or enlarg*)).tw. (40106)
83 BPH.tw. (19805)
84 (PSA or prostate-specific antigen* or prostatic-specific antigen* or gamma-seminoprotein* or (hK3 adj1 Kallikrein) or semenogelase or seminin).tw. (76299)
85 or/78-84 (315938)
86 fatty acids/ (172045)
87 (eicosapentanoic acid* or icosapentaenoic acid* or icosapentaenoate or omega-3-eicosapentaenoic acid* or timnodonic acid* or eicosapen).tw. (600)
88 ("5,8,11,14,17-Eicosapentaenoic Acid" or "5,8,11,14,17-Icosapentaenoic Acid").tw. (143)
89 EPA.tw. (24393)
90 (docosahexaenoic acid* or docosahexaenoate or dhasco).tw. (18092)
91 dha.tw. (20493)
92 ("omega 3" or omega3 or n-3 fatty acid* or n3 fatty acid* or n-3 polyunsaturated fatty acid* or n-3 poly-unsaturated fatty acid* or n3 polyunsaturated fatty acid* or n3 poly-unsaturated fatty acid* or n-3 PUFA or n3 PUFA or PUFAs).tw. (35392)
93 (Maxepa or Omacor).tw. (998)
94 or/86-93 (230884)
95 85 and 94 (851)
96 fishes/ (141926)
97 exp food/ (1803802)
98 exp diet/ (439211)
99 96 and (97 or 98) (21782)
100 (fish$2 or fishoil* or shellfish$2 or shell fish$2 or seafood* or sea food* or marine*).tw. (403998)
101 99 or 100 (409563)
102 85 and 101 (2072)
103 95 or 102 (2769)
104 exp Animals/ not (exp Animals/ and Humans/) (8758181)
105 103 not 104 (2474)
106 (comment or editorial or interview or letter or news).pt. (2839640)
107 105 not 106 (2450)
108 107 use amed (7)
109 37 or 77 or 108 (2515)
110 remove duplicates from 109 (1778) [UNIQUE RECORDS]
111 110 use prmz (821) [MEDLINE RECORDS]
112 110 use emczd (956) [EMBASE RECORDS]
113 110 use amed (1) [AMED RECORD]

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Cochrane Library

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Date Run: 21/07/14 13:43:26.496
Description: Final 2014 Jul 21
ID Search Hits
#1 [mh "Prostatic Neoplasms"] 3374
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#4 [mh Prostate/de] 103
#5 [mh "Prostatic Hyperplasia"] 1361
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#10 {or #1-#9} 7311
#11 [mh ^"Fatty Acids, Omega-3"] 1258
#12 [mh "Eicosapentaenoic Acid"] 647
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#15 EPA:ti,ab,kw 830
#16 [mh "Docosahexaenoic Acids"] 694
#17 (docosahexaenoic next acid*) or docosahexaenoate or dhasco:ti,ab,kw 1399
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#19 "omega 3" or omega3 or (("n-3 fatty" or "n3 fatty" or "n-3 polyunsaturated fatty" or "n-3 poly-unsaturated fatty" or "n3 polyunsaturated fatty" or "n3 poly-unsaturated fatty") next acid*) or "n-3 PUFA" or "n3 PUFA" or PUFAs:ti,ab,kw 2804
#20 Maxepa or Omacor:ti,ab,kw 106
#21 {or #11-#20} 3714
#22 #10 and #21 21
#23 [mh Fishes] 218
#24 [mh Food] or [mh Diet] 29205
#25 #23 and #24 155
#26 fish or fishes or fishoil* or shellfish* or (shell next fish*) or seafood* or (sea next food*) or marine*:ti,ab,kw 3060
#27 #25 or #26 3064
#28 #10 and #27 17
#29 #22 or #28 33
DSR - 3
DARE - 2
CENTRAL - 27
Cochrane Groups - 1 *(did not download)*

CINAHL

2014 Jul 21

#	Query	Limiters/Expanders	Results
S38	S35 NOT S36	Limiters: Exclude MEDLINE records Expanders: Apply related words Search modes: Boolean/Phrase	57
S37	S35 NOT S36	Expanders: Apply related words Search modes: Boolean/Phrase	113
S36	PT comment or editorial or interview or letter or news	Expanders: Apply related words Search modes: Boolean/Phrase	306747
S35	S31 NOT S34	Expanders: Apply related words Search modes: Boolean/Phrase	127
S34	S32 NOT (S32 AND S33)	Expanders: Apply related words Search modes: Boolean/Phrase	26845
S33	(MH "Human")	Expanders: Apply related words Search modes: Boolean/Phrase	848532
S32	(MH "Animals+")	Expanders: Apply related words Search modes: Boolean/Phrase	29062
S31	S22 OR S30	Expanders: Apply related words Search modes: Boolean/Phrase	130

(continued)

Appendix A (continued)

#	Query	Limiters/Expanders	Results
S30	S10 AND S29	Expanders: Apply related words Search modes: Boolean/Phrase	55
S29	S23 OR S27 OR S28	Expanders: Apply related words Search modes: Boolean/Phrase	5992
S28	TI (fish or fishes or fishoil* or shellfish* or (shell n1 fish*) or seafood* or (sea n1 food*) or marine*) OR AB (fish or fishes or fishoil* or shellfish* or (shell n1 fish*) or seafood* or (sea n1 food*) or marine*)	Expanders: Apply related words Search modes: Boolean/Phrase	4355
S27	S24 AND (S25 OR S26)	Expanders: Apply related words Search modes: Boolean/Phrase	2413
S26	(MH "Diet+")	Expanders: Apply related words Search modes: Boolean/Phrase	48485
S25	(MH "Food+")	Expanders: Apply related words Search modes: Boolean/Phrase	66225
S24	(MH "Fish")	Expanders: Apply related words Search modes: Boolean/Phrase	2413
S23	(MH "Seafood+")	Expanders: Apply related words Search modes: Boolean/Phrase	2998
S22	S10 AND S21	Expanders: Apply related words Search modes: Boolean/Phrase	96
S21	S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20	Expanders: Apply related words Search modes: Boolean/Phrase	5246
S20	TI (Maxepa or Omacor) OR AB (Maxepa or Omacor)	Expanders: Apply related words Search modes: Boolean/Phrase	22
S19	TI ("omega 3" or omega3 or (("n-3 fatty" or "n3 fatty" or "n-3 polyunsaturated fatty" or "n-3 poly-unsaturated fatty" or "n3 polyunsaturated fatty" or "n3 poly-unsaturated fatty") n1 acid*) or "n-3 PUFA" or "n3 PUFA" or PUFAs) OR AB ("omega 3" or omega3 or (("n-3 fatty" or "n3 fatty" or "n-3 polyunsaturated fatty" or "n-3 poly-unsaturated fatty" or "n3 polyunsaturated fatty" or "n3 poly-unsaturated fatty") n1 acid*) or "n-3 PUFA" or "n3 PUFA" or PUFAs)	Expanders: Apply related words Search modes: Boolean/Phrase	2309
S18	TI dha OR AB dha	Expanders: Apply related words Search modes: Boolean/Phrase	633
S17	TI ((docosahexaenoic n1 acid*) or docosahexaenoate or dhasco) OR AB ((docosahexaenoic n1 acid*) or docosahexaenoate or dhasco)	Expanders: Apply related words Search modes: Boolean/Phrase	684
S16	(MH "Docosahexaenoic Acids")	Expanders: Apply related words Search modes: Boolean/Phrase	975
S15	TI EPA OR AB EPA	Expanders: Apply related words Search modes: Boolean/Phrase	801
S14	TI ("5,8,11,14,17-Eicosapentaenoic Acid" or "5,8,11,14,17-Icosapentaenoic Acid") OR AB ("5,8,11,14,17-Eicosapentaenoic Acid" or "5,8,11,14,17-Icosapentaenoic Acid")	Expanders: Apply related words Search modes: Boolean/Phrase	1
S13	TI ((eicosapentanoic n1 acid*) or (icosapentaenoic n1 acid*) or icosapentaenoate or ("omega-3-eicosapentaenoic" n1 acid*) or (timnodonic n1 acid*) or eicosapen) OR AB ((eicosapentanoic n1 acid*) or (icosapentaenoic n1 acid*) or icosapentaenoate or ("omega-3-eicosapentaenoic" n1 acid*) or (timnodonic n1 acid*) or eicosapen)	Expanders: Apply related words Search modes: Boolean/Phrase	13
S12	(MH "Eicosapentaenoic Acid")	Expanders: Apply related words Search modes: Boolean/Phrase	678
S11	(MH "Fatty Acids, Omega-3")	Expanders: Apply related words Search modes: Boolean/Phrase	3404
S10	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9	Expanders: Apply related words Search modes: Boolean/Phrase	13411
S9	TI ((PSA or prostate-specific antigen* or prostatic-specific antigen* or gamma-seminoprotein* or (hK3 N1 Kallikrein) or semenogelase or seminin)) OR AB ((PSA or prostate-specific antigen* or prostatic-specific antigen* or gamma-seminoprotein* or (hK3 N1 Kallikrein) or semenogelase or seminin))	Expanders: Apply related words Search modes: Boolean/Phrase	2125

(continued)

Appendix A (continued)

#	Query	Limiters/Expanders	Results
S8	(MH "Prostate-Specific Antigen")	Expanders: Apply related words Search modes: Boolean/Phrase	2517
S7	TI BPH OR AB BPH	Expanders: Apply related words Search modes: Boolean/Phrase	401
S6	TI (((prostate or prostatic) N3 (hyperplasia* or adenoma* or hypertroph* or enlarg*))) OR AB (((prostate or prostatic) N3 (hyperplasia* or adenoma* or hypertroph* or enlarg*)))	Expanders: Apply related words Search modes: Boolean/Phrase	713
S5	(MH "Prostatic Hypertrophy")	Expanders: Apply related words Search modes: Boolean/Phrase	1332
S4	(MH "Prostate/DE")	Expanders: Apply related words Search modes: Boolean/Phrase	42
S3	TI (((prostate or prostatic) N3 (anticancer* or anti-cancer* or anticarcinogen* or anti-carcinogen* or antineoplas* or anti-neoplas* or chemoprevent* or chemo-prevent* or (tumo#r N2 suppress*)))) OR AB (((prostate or prostatic) N3 (anticancer* or anti-cancer* or anticarcinogen* or anti-carcinogen* or antineoplas* or anti-neoplas* or chemoprevent* or chemo-prevent* or (tumo#r N2 suppress*))))	Expanders: Apply related words Search modes: Boolean/Phrase	59
S2	TI (((prostate or prostatic) N3 (cancer* or carcinoid* or carcinoma* or carcinogen* or adenocarcinoma* or adeno-carcinoma* or malignan* or neoplasia* or neoplasm* or sarcoma* or tumour* or tumor*))) OR AB (((prostate or prostatic) N3 (cancer* or carcinoid* or carcinoma* or carcinogen* or adenocarcinoma* or adeno-carcinoma* or malignan* or neoplasia* or neoplasm* or sarcoma* or tumour* or tumor*)))	Expanders: Apply related words Search modes: Boolean/Phrase	7,608
S1	(MH "Prostatic Neoplasms")	Expanders: Apply related words Search modes: Boolean/Phrase	10,199

Appendix B

Preclinical Studies Reference List

1. Apte S, Friedrichs W, Hursting S, et al. Delayed progression to hormone-independent prostate cancer through modulation of mTOR by omega-3 fatty acids. *Cancer Res*. 2010;70(8 suppl 1). Paper presented at:101st Annual Meeting of the American Association for Cancer Research; April 17-21, 2010; Washington, DC.
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