The relevance of serum levels of long chain omega-3 polyunsaturated fatty acids and prostate cancer risk: A meta-analysis

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Abstract

Objective: Our objective was to systematically analyze the evidence for an association between serum level long chain omega-3 polyunsaturated fatty acid (n-3 PUFA) and prostate cancer risk from human epidemiological studies.
Study Procedures: We searched biomedical literature databases up to November 2011 and included epidemiological studies with description of long chain n-3 PUFA and incidence of prostate cancer in humans. Critical appraisal was done by two independent reviewers. Data were pooled using the general variance-based method with random-effects model; effect estimates were expressed as risk ratio with 95% confidence interval (CI). Heterogeneity was assessed by Chi^2 and quantified by I^2, publication bias was also determined.
Results: In total, 12 studies were included. Significant negative association was noted between high serum level of n-3 PUFA docosapentaenoic acid (DPA) and total prostate cancer risk (RR:0.756; 95% CI 0.599, 0.955; $p = 0.019$). Likewise, a positive association between high blood level of fish oil contents, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), and high-grade prostate tumour incidence (RR:1.381; 95% CI 1.050, 1.817; $p = 0.021$) was noted; however, this finding was evident only after adjustment was done on interstudy variability through the removal of a lower quality study from the pool.
Conclusions: High serum levels of long chain n-3 PUFA DPA is associated with reduced total prostate cancer risk. While high blood level of EPA and DHA is possibly associated with increased high-grade prostate tumour risk.

Introduction

Due to widespread use of prostate-specific antigen (PSA) screening, more prostate cancer is being detected. To find ways to prevent prostate cancer, several studies have tried to identify risk factors (i.e., lifestyle and diet). Researchers have studied the effects of long-chain omega-3 polyunsaturated fatty acids (n-3 PUFA), found in marine animals, on the prevalence of prostate cancer. These mechanisms of n-3 PUFA regulate inflammation via the eicosanoid pathway[1-4] and modify androgen production.[5] In particular, dietary intake of long-chain n-3 PUFA or its individual components (eicosapentaenoic acid [EPA], docosahexaenoic acid [DHA], docosapentaenoic acid [DPA]), have been proposed to have an association with prostate cancer risk; however, these results have been inconsistent, largely variable and heterogeneous.[6-9] These inconsistent results were mainly due to research variations in dietary assessment techniques and under- or over-reporting of values, which decreased the accuracy of measuring individual's fatty acid intake.[10,11] Experts have suggested that levels of fatty acids in blood, tissue or erythrocyte membranes could provide a more reliable method of estimating fatty acid consumption.[12-16] We conducted a meta-analysis to quantitatively estimate the correlation between blood levels of long chain n-3 PUFA and its derivatives with the incidence of prostate cancer in epidemiological studies.

Methods

We searched biomedical electronic databases, regardless of language. MEDLINE, UNBOUND MEDLINE, EMBASE, Science Direct, OVID, Proquest (database of dissertation and thesis) and the Cochrane Library were searched up to November 2011. MEDLINE Medical Subject Heading (MeSH) terms used were "omega 3 fatty acids" AND "prostate neoplasm." Common keyword searches were "prostate cancer," "carcinoma," "neoplasm," "tumor," "omega," "long chain fatty acids" and "polyunsaturated." References from studies that met our inclusion criteria and review articles or textbooks were searched for potentially relevant titles. External peer reviewers were asked to identify additional relevant studies. Industry/nutrition experts were also inquired to obtain unpublished data.

We included prospective or retrospective case control studies of human population, where the blood level of long

chain n-3 PUFA (DHA, DPA and EPA) was determined as exposure and incidence of prostate cancer was analyzed as outcome. All included studies provided effect estimates with corresponding confidence intervals pertaining to comparison between high long chain n-3 PUFA blood level and the reference group (lowest blood level). This unvarying method of comparison among the studies eliminated the differences of blood level n-3 PUFA source and ranges described in each study. Studies dealing with tissue n-3 PUFA levels were not included, since the sampling procedure was complex and usually done on high-risk patients, which could affect the reliability of effect estimates. Animal and in-vitro studies were excluded because correlation with in-vivo human physiologic outcome is uncertain. Cross-sectional and ecologic analyses were excluded, since these studies were unable to provide informative effect estimates.[17]

Two physician reviewers independently evaluated all citations and abstracts, and then they requested all the relevant full-text articles (Fig. 1). All articles obtained were independently reviewed by two reviewers knowledgeable in principles of critical appraisal. When discrepancy of evaluation arose, both reviewers resolved disagreements; a senior physician resolved unsettled issues. Articles retrieved were critically appraised and scored according to the National Health Service (NHS-UK) recommendation for review of qualitative studies.[18] The maximum score was 11 points; studies that scored below 8 were excluded. Then, we used the Newcastle-Ottawa Quality Assessment Scale (NOQAS) of Cochrane Collaboration[19] to rate each included study and enhance quality assessment, and to rank studies when heterogeneity was noted.

The general variance-based method was used to analyze the cohort studies, because variance estimates were based on adjusted measures of effect with 95% confidence interval (CI) that account for confounding variables and known to be superior in pooling observational data.[19] Relative risk (RR) or odds ratio (OR) and corresponding CI, with adjustments for confounding variables, were used to estimate the risk ratio of prostate cancer incidence and subcategories (advanced and high grade type prostate tumour) with highest blood level of long chain omega-3 fatty acids component (DPA, DHA, EPA) versus the reference group. Only the most recent and comprehensive data were included when a study was published at several times and on different dates.

We used Cochran's chi-square test (Q) and I squared (I^2) to assess inter-study heterogeneity and variance, respectively.[20] In cases of heterogeneity ($p < 0.1$), the source was identified by performing subgroup analyses on the basis of important differences in study design (retrospective case control vs. nested case-control). Afterwards, sensitivity analysis was repeated by excluding the study with the lowest NOQAS from the pool to acquire homogeneous pool estimates.

The random effect model was used to determine pooled effect estimates, since this model is more conservative.[21] For analyzing the summation effect of long chain n-3 PUFA (DPA+DHA+EPA) and commercially available fish oil n-3 PUFA content (DHA+EPA) with prostate cancer incidence
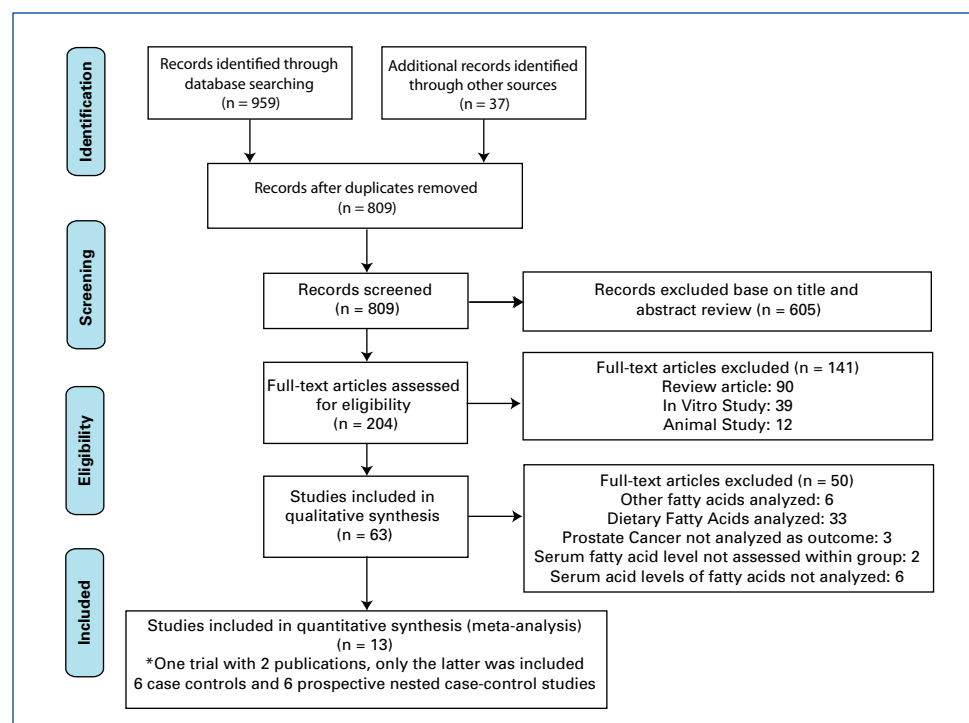

Fig. 1. Prisma chart literature search process and result.

and its subcategories, we used a mixed effect analysis- random effects model to combine studies within each subgroup of long chain n-3 PUFA. The Comprehensive Meta Analysis software version 2 (Biostat, Englewood, NJ)[22] and RevMan5[23] were used for the statistical analysis of pooled data and construction of forest plots. Publication bias was examined using Egger's regression intercept,[24] Begg-Mazumdar rank correlation[25] analysis and visual inspection of funnel plots.[26]

Results

In total, we included 12 articles for this meta-analysis: 6 case-control studies[27-32] and 6 nested case control studies (Table 1).[33-38] All studies uniformly compared prostate cancer risk with the groups of involved population with the highest blood level of long chain n-3 PUFA and the reference group (lowest blood level). Most studies analyzed risk of prostate cancer development as part of their studies' outcome.[27-37] Four studies included advanced stage (defined as extension of tumour through the capsule) prostate cancer.[28,35-37] Five studies included high-grade tumour (defined as tumour Gleason score ≥7) in their analysis of outcome.[30,35-38] The age range of the study population was 40 to 86 years old. Overall, we analyzed 4516 prostate cancer cases and 5728 matching controls.

Blood level omega-3 PUFA and prostate cancer risk

Visual inspection of funnel plot showed publication bias less likely (Fig. 2). Results showed that the pooled estimates of long chain n-3 PUFA DPA have a significant association with total prostate cancer incidence (pooled RR: 0.756; CI 0.599, 0.955; $p = 0.019$) (Fig. 3). In the homogeneous studies ($p = 0.566$), there were no study variations ($I^2 = 0\%$), and no publication bias in the Begg ($p = 1.0$) and Egger's regression intercept ($p = 0.54$) (Table 2.1). When subgroup analysis was done by method of study (retrospective vs. prospective), the significant finding was retained in the prospective studies (pooled RR: 0.773; CI 0.605, 0.988; $p = 0.040$). High blood levels of total n-3 PUFA or other derivatives (together and individually) had no significant association to total prostate cancer risk, advanced prostate cancer and high-grade prostate tumour (Table 3).

Significant heterogeneity was noted on the analysis of blood level n-3 PUFA DHA and EPA with total prostate cancer risk and high-grade prostate tumours (Table 2.2, Table 4); therefore the validity of the result was questioned. The inter-study variation ranged from 32% to 53%. Source of heterogeneity was identified (Table 2.2) and a nested case-control study[34] was removed from the pooled estimate which resulted to reduced heterogeneity and variation (I^2).

Reviewing the summation effect of fish oil content long chain n-3 PUFA (DHA+EPA) on prostate cancer develop-

ment, we found a significant positive association (pooled RR: 1.39; CI 1.07, 1.80; $p = 0.021$) (Fig. 4) with high-grade prostate cancer. Adjusted inter-study heterogeneity was not significant ($p = 0.291$) with a small degree of inter-study variation ($I^2 = 17.6\%$). Publication bias of the respective n-3 PUFA subgroup analysis was not evident using Begg ($p = 0.734$), Egger's ($p = 0.265, 0.952$) test (Table 4) and upon visual inspection of the funnel plot (data not shown).

Discussion

Randomized clinical trials have not been done to clarify the role of n-3 PUFA in prostate cancer development due to ethical considerations and methodological limitations; as such, we investigated this relationship using the best credible epidemiological data available – case controls. Another important aspect in this meta-analysis is that all included studies were executed in the 1990s when PSA screening was utilized for early detection of prostate cancer.

After an extensive review, we found a significant negative association between high blood n-3 PUFA DPA level and total risk of prostate cancer. DPA is found in whale meat, seal oil and, to a lesser extent, in marine fatty fish oil together with other long chain n-3 PUFA series (DHA and EPA).[39] Currently, few studies have been conducted to examine the biophysiological effect of DPA because of production costs. Human studies are lacking; most studies are in-vitro or with animal subjects.[40] In the study by Wang and colleagues, the finding of high serum level DPA is a result of in-vivo biochemical conversion rather than mere high dietary exposure, since the commercially available supplement of long chain n-3 PUFA DPA is not common or readily available.[40] Moreover, in the subgroup analysis of the pooled prospective studies, the significant association was retained; this illustrates the association as an effect of long-term lipid metabolism rather than short-term dietary exposure. Studies have shown that humans are able to biosynthesize DPA mainly through bioconversion from EPA by enzymes fatty acid elongase-2 and 5, and could be retro-converted to EPA in the liver and kidney.[41-43] The mechanism of the protective effect of DPA on prostate cancer may be explained by biochemical processes involving: reduced prostacyclin production, expression of inflammatory genes and TNF-induced necrotic cell death; competition with cycloxygenase 2 (COX2) enzymes resulting to anti-neoplastic activity via proapoptotic pathway; and inhibition of angiogenesis.[44-49] Detection of such association may suggest that serum level DPA implicates individual genetic difference in biochemical characteristics of enzymatic activities, which may be further investigated as a probable new serum biomarker for prostate cancer risk assessment in the future.

Heterogeneity was noted in the analysis of association of blood level DHA and EPA with prostate cancer and high-
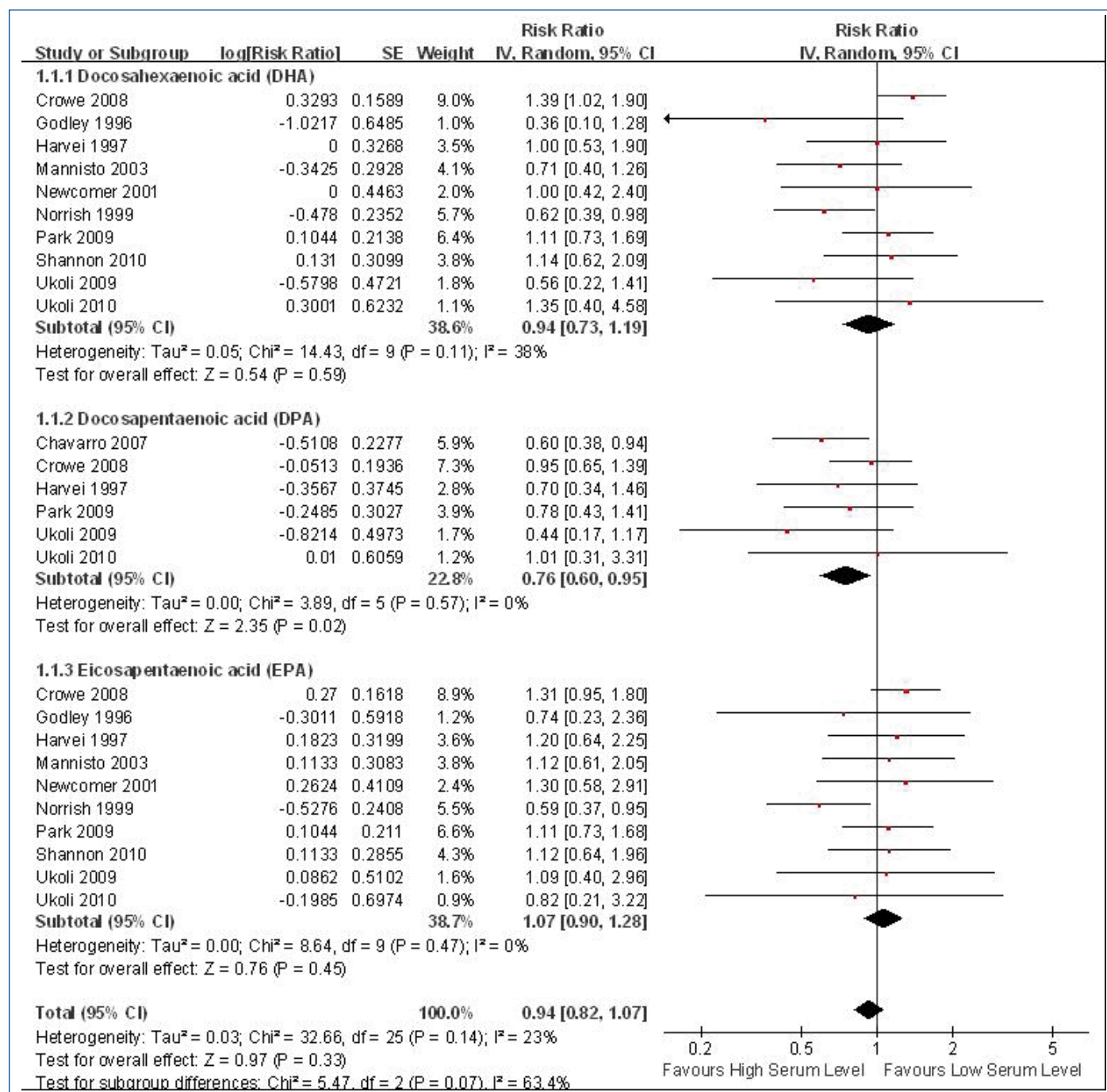
Fig. 2. Forest plot of pooled effect of blood level omega-3 polyunsaturated fatty acid (PUFA) on total prostate cancer risk.

grade prostate tumour. The source of heterogeneity was mainly from the nested case cohort of "The Physician's Health Study."[3] The authors acknowledged that their subjects were more knowledgeable and provided more reliable information. However, this group may have a generally higher DHA and EPA intake which affected the study's results because of their increased awareness towards healthy practices. The study also failed to present adjustments for confounding variables, such as family history, body mass index and racial ethnicity, which were established risk factors for prostate cancer. When this study was excluded, a significant positive association was noted on fish oil containing long chain n-3 PUFA (EPA+DHA) with high grade prostate cancer (Table 4). Factors to consider on this relative association is the healthier lifestyle of patients taking fish oil. These patients tend to be more health conscious,

Table 1. Summary of Studies Characteristics Included in the Meta-Analysis

Authors (Year)	Source	Study design	Age of study population (Case/control)	Years of follow-up	Ascertain of cases (Prostate Ca)	Blood omega-3 fatty acid level determination	Relative risk* (CI) omega-3	Level of comparison used	Quality score (NOQAS**) Selection (S)	Comparability (C)	Exposure (E)	Quality score (NHS++)	Adjustment variables
									S (4)	C (2)	E (3)		
Harvei 1997[33]	Norway	Nested Case Control	Ave. 50 yr (141/282)	19.2 years (Ave 11.6)	Cancer registries	Serum fatty acids	Total Risk EPA 1.2 (0.6-2.1) DHA 1.0 (0.5-1.8) DPA 0.7 (0.3-1.3)	Quartile	3	2	3	9/11	Age, area of residence
Mannisto 2003[34]	Finland	Nested Case Control	50-69 yr (198/198)	5-10 years	Cancer registry and histo-pathology review	Serum fatty acids	Total risk EPA 1.12 (0.61-2.04) DHA 0.71 (0.40- 1.26)	Quartile	2	2	3	8/11	Age, Area of residence (urban/ rural), level of education, body mass index, alcohol consumption, and the number of years of smoking.
Chavarro 2007[35]	US	Nested Case Control	40-84 yr (476/476)	13 years	Hospital Record and histo-pathology review	Blood level fatty acids	Total risk DPA 0.6 (0.38-0.93) EPA 0.57 (0.36-0.92) DHA 0.60 (0.39-0.93) Advance DPA 0.72 (0.3-1.73) EPA 1.27 (0.49-3.29) DHA 0.98 (0.39-2.50) High grade DPA 0.30 (0.12-0.80) EPA 0.42 (0.15-1.14) DHA 0.53 (0.21-1.31)	Quintile	2	1	3	9/11	Age, smoking status at baseline, and length of follow-up
Crowe 2008[36]	Nether-lands	Nested Case Control	53-67 yr (962/1061)	4.2 years	National & regional cancer registry	Blood phospholipid	Total risk EPA 1.31 (0.96-1.81) DHA 1.39 (1.02-1.90) DPA 0.95 (0.65-1.39) Advance EPA 0.99 (0.49-2.01) DHA 1.22 (0.62-2.40) DPA 0.91 (0.42-2.00) High grade EPA 2.00 (1.07-3.76) DHA 1.41 (0.76-2.62) DPA 0.71 (0.35-1.46)	Quintile	2	2	3	9/11	Age, BMI, smoking, alcohol intake, level of education, marital status, and physical activity

*Relative risks with corresponding 95% confidence interval were derived comparing the prostate cancer incidence among the population group with highest blood level n-3 PUFA versus lowest blood level PUFA
**Newcastle-Ottawa Quality Assessment Score; ++National Health Service; UK recommended critical appraisal of Case-control; BMI: body mass index.

Table 1. Summary of Studies Characteristics Included in the Meta-Analysis (cont'd)

Authors (Year)	Source	Study design	Age of study population (Case/Control)	Years of follow-up	Ascertain of cases (Prostate Ca)	Blood omega-3 fatty acid level determination	Relative risk* (CI) omega-3	Level of comparison used	Quality score (NOQAS**) Selection (S) Comparability (C) Exposure (E) S (4)	C (2)	E (3)	Quality score (NHS++)	Adjustment variables
Park 2009[37]	USA	Nested Case Control	45-75 yr (376/729)	10 years	Tumor registry	Erythrocyte membrane fatty acids	Total risk EPA 1.11 (0.73-1.67) DHA 1.11 (0.73-1.69) DPA 0.78 (0.43-1.41) Advance/high grade EPA 1.61 (0.79-3.25) DHA 1.05 (0.51-2.16) DPA 1.13 (0.33-3.82)	Quartile and Tertile	2	2	3	10/11	Age, area of residence, race/ethnicity, family history of prostate cancer, BMI, level of education, hour of fasting, date and time of blood draws,
Brasky 2011[38]	USA	Nested Case Control	55-84 yr (1658/1803)	7 years	End study prostate biopsies	Serum fatty acids	Low Grade EPA 1.01 (0.83-1.24) DHA 1.18 (0.97-1.44) High Grade EPA 1.09 (0.63-1.86) DHA 2.50 (1.34-4.65)	Quartile	4	2	3	9/11	Age, race, family history of prostate cancer, diabetes, BMI, alcohol, and treatment arm.
Norrish 1999[32]	New Zealand	Nested Case Control (from PCPT)	40-80 yr (317/480)	N/A	Histo-pathology	Erythrocyte membrane fatty acids	Total Risk EPA 0.59 (0.37-0.95) DHA 0.62 (0.39-0.98) Advance EPA 0.54 (0.31-0.98) DHA 0.66 (0.39-1.13)	Quartile	3	2	3	9/11	Age, height, total non-steroidal anti-inflammatory drug use, socio-economic status, and food frequency questionnaire-estimated intake of total polyunsaturated fat
Shannon 2010[30]	USA	Case Control	50-86 yr (127/183)	N/A	Histo-pathology	Erythrocyte Fatty membrane fatty acids	Total risk EPA 1.12 (0.64-1.96) DHA 1.14 (0.62-2.09) High grade EPA 0.83 (0.39-1.75) DHA 1.06 (0.48-2.32)	Tertile	3	2	3	9/11	Age, BMI, race, and family history of prostate cancer
Godley 1996[27]	USA	Case Control	>45 yr (89/38)	N/A	Histo-pathology	Erythrocyte membrane fatty acids	Total Risk EPA 0.74 (0.23-2.33) DHA 0.36 (0.10-1.27)	Quartile	3	2	2	8/11	Age and Race
New-comer 2001[28]	USA	Case Control	41-66 yr (67/156)	N/A	Histo-pathology	Erythrocyte membrane fatty acids	Total risk EPA 1.3 (0.6-3.0) DHA 1.0 (0.4-2.3)	Quartile	3	1	3	8/11	Age

*Relative risks with corresponding 95% confidence interval were derived comparing the prostate cancer incidence among the population group with highest blood level n-3 PUFA versus lowest blood level PUFA
**Newcastle-Ottawa Quality Assessment Score; ++National Health Service- UK recommended critical appraisal of Case-control; BMI: body mass index.

Table 1. Summary of Studies Characteristics Included in the Meta-Analysis (cont'd)

Authors (Year)	Source	Study design	Age of study population (Case/Control)	Years of follow-up	Ascertain of cases (Prostate Ca)	Blood omega-3 fatty acid level determination	Relative risk* (CI) omega-3	Level of comparison used	Quality score (NOQAS**) Selection (S) Comparability (C) Exposure (E)			Quality score (NHS++)	Adjustment variables
									S (4)	C (2)	E (3)		
Ukoli 2009[29]	Nigeria	Case Control	>=45 (66/226)	N/A	Histo-pathology	Serum fatty acids	Total risk EPA 1.09 (0.4-2.96) DPA 0.44 (0.17-1.19) DHA 0.56 (0.22-1.40)	Quartile	3	2	3	9/11	Age, level of education, family history of prostate cancer, and waist-hip ratio.
Ukoli 2010[31]	Nigeria	Case Control	>=45 (48/96)	N/A	Histo-pathology	Serum fatty acids	Total Risk EPA 0.82 (0.21-3.24) DPA 1.01 (0.31-3.33) DHA 1.35 (0.40-4.61)	Quartile	3	2	3	9/11	Age, level of education, family history of prostate cancer, and waist-hip ratio.

*Relative risks with corresponding 95% confidence interval were derived comparing the prostate cancer incidence among the population group with highest blood level n-3 PUFA versus lowest blood level PUFA
**Newcastle-Ottawa Quality Assessment Score; ++National Health Service- UK recommended critical appraisal of Case-control.

which may produce a co-founding factor of early detection via PSA screening due to better health follow-up and health care access. However, the detection of high-grade prostate tumour instead of indolent or total prostate cancer risk among this subgroup is presumed to be due to a biochemical process in the prostate tissue. Since, it is well-illustrated in epidemiological studies that increased prostate cancer incidence due to early detection by vast PSA screening is more significant for general risk or detection of indolent type of prostate cancery.[50-52]

The finding of an association between EPA+DHA with high-grade prostate tumour was quite similar with the findings by the Prostate Cancer Prevention Trial (PCPT).[50] Nonetheless, there is still debate about whether finasteride induces the development of high-grade prostate tumour or results to a better detection rate by reducing prostate size.[50] As mentioned earlier, there are inconsistencies regarding the effects of long-chain PUFA, particularly EPA and DHA, in the development of prostate cancer. Some studies have recognized the effects of n-3 PUFA via eicosanoid pathway in cancer prevention, while others have implicated the role of dietary fat in changing the androgen milieu as a causative factor for prostate cancer. The detection of high-grade prostate tumour instead of indolent or total prostate cancer risk was presumed to be due to a biochemical process in the prostate tissue. The since increased early detection of prostate cancer due to PSA screening is more frequent in general risk or indolent type of cancer rather than in the high-grade subtype only.[51,52]

Reports have also shown that marine fish contaminated with environmental toxins, such as polychlorinated biphenyls or methylmercury compounds, can disrupt androgen and estrogen balance and could be linked to high-grade prostate cancer.[53-54] Furthermore, the presence of long chain n-3 PUFA (DHA and EPA) in the prostate cell's beta-oxidative metabolic process leads to the formation of lipid hydroperoxides in the microenvironment of the cell; this can generate reactive species.[55-56] With chronic exposure to these reactive molecules, the prostate cell can become dysplastic and develop into an aggressive cell.

In this aspect, the possible role of both EPA and DHA needs to be examined further for their use as biomarkers for aggressive disease and to see if a reduction of these n-3 PUFA can decrease the risk. Possible reasons why EPA and DHA, but not DPA, are implicated in aggressive prostate cancer remain to be determined. The association of serum DPA in prostate cancer development still needs to be examined further, since lipid metabolism is far more intricate and genetic variations in individuals may be involved.[57]
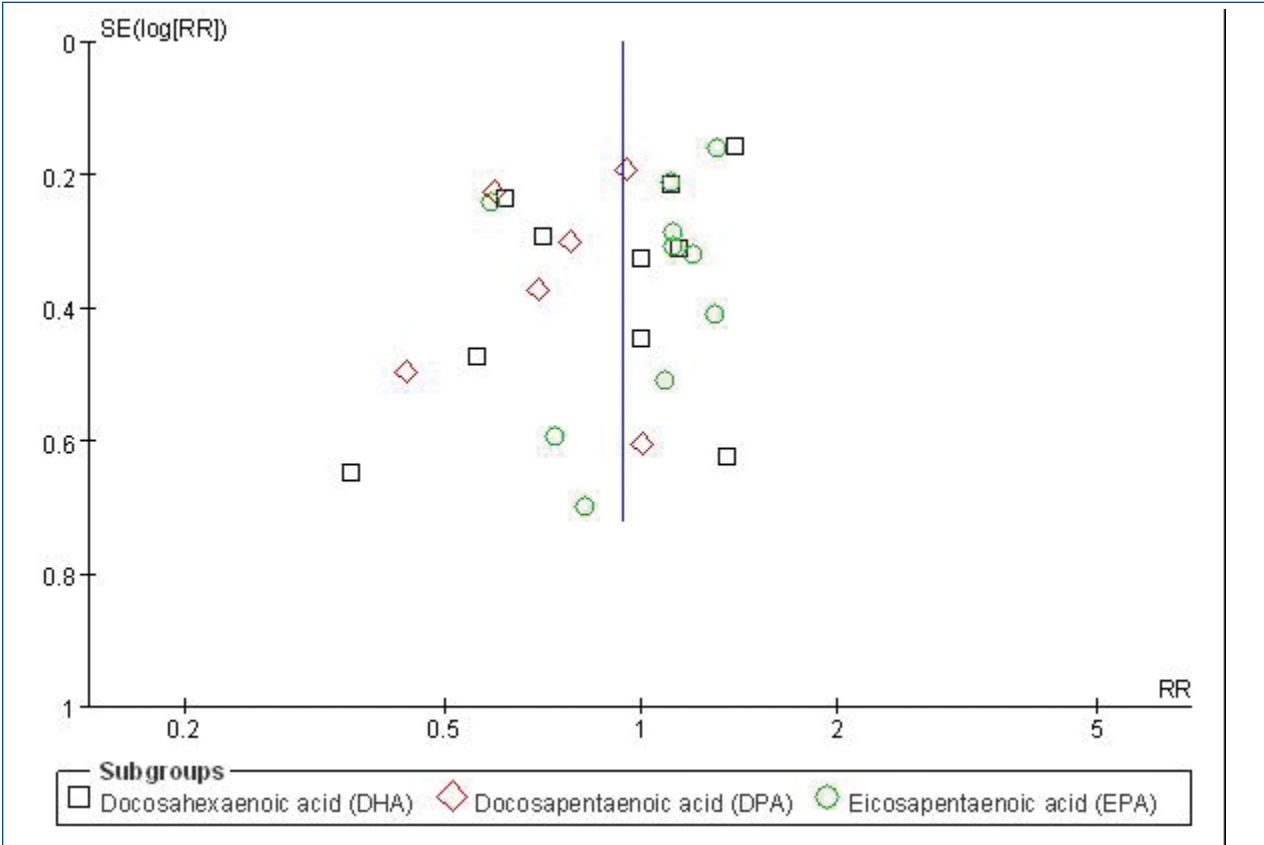
Fig. 3. Publication bias determination using funnel plot.
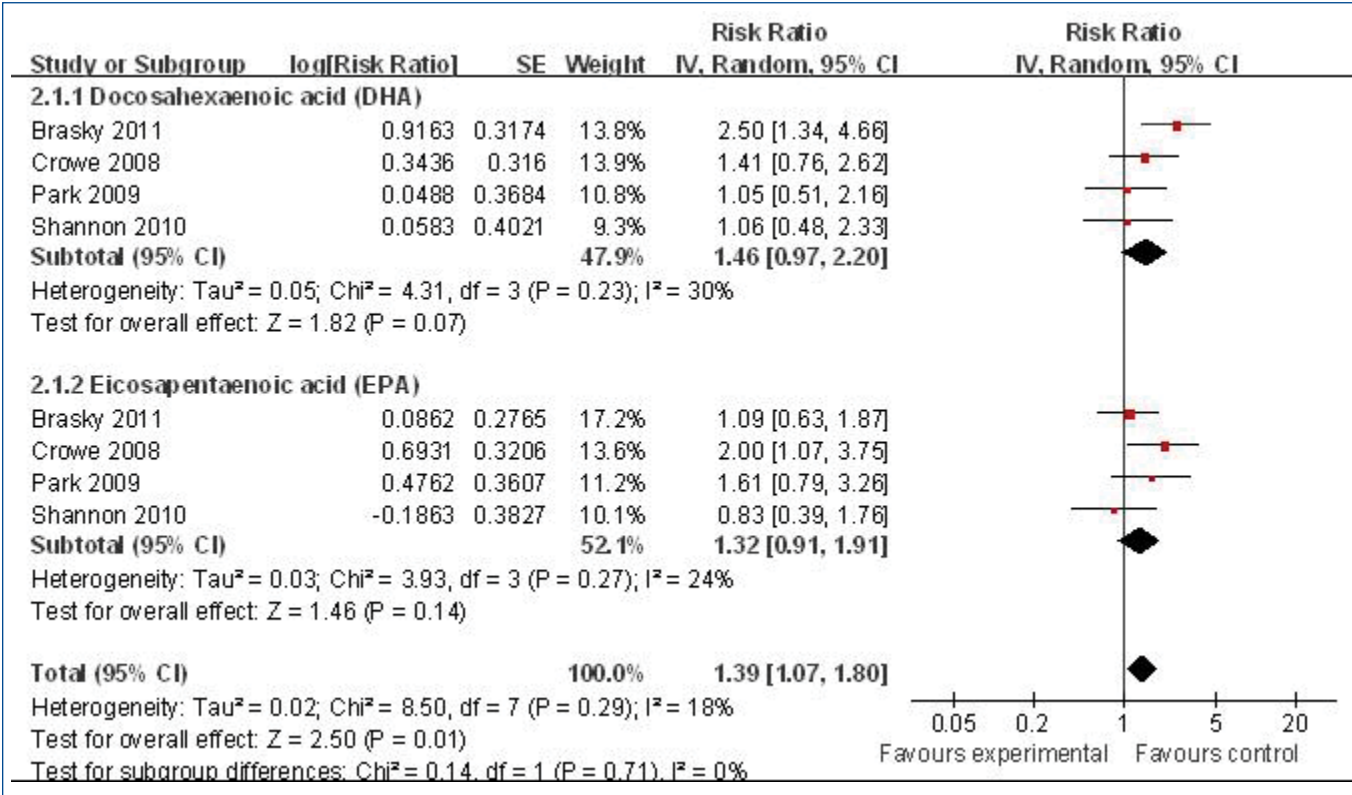

Fig. 4. Forest plot of pooled effect of blood level omega-3 polyunsaturated fatty acid (PUFA) high-grade prostate tumour.

Table 2.1 Blood level omega-3 poly-unsaturated fatty acids vs. total prostate risk random effect analysis model

Groups		Effect size and 95% interval			Test of null (2-Tail)		Heterogeneity^				Tau-squared			Publication bias	
Omega-3 derivatives	# of Study	Point Estimates	Lower Limit	Upper Limit	Z-value	P-value	Q-value	df	p-value	I²	Tau²	Standard Error	Variance	Begg	Egger
DPA	6	0.756	0.599	0.955	-2.347	0.019	3.883	5	0.566	0.000	0.000	0.060	0.004	1.000	0.540
DHA	11	0.876	0.685	1.119	-1.059	0.290	18.991	10	0.040	47.343	0.072	0.073	0.005	0.436	0.239
DHA†	10	0.935	0.733	1.194	-0.538	0.591	14.450	9	0.107	37.716	0.053	0.069	0.005	0.211	0.127
EPA	11	0.971	0.784	1.204	-0.264	0.792	14.741	10	0.142	32.162	0.039	0.056	0.003	0.533	0.671
EPA†	10	1.070	0.898	1.275	0.762	0.446	8.656	9	0.470	0.000	0.000	0.041	0.002	0.211	0.502
(DHA+DPA+EPA)*		0.942	0.834	1.064	-0.962	0.336	32.676	25	0.139	23.492	0.026	0.031	0.001		
(DHA+EPA)*		1.022	0.887	1.179	0.306	0.760	23.410	19	0.220	18.840	0.019	0.034	0.001		

^Inter-study heterogeneity was tested by Cochrane's Q (Chi²) at a significance level of P<0.10 and quantified by I², where I² ≥ 50 % is considered to be evidence of substantial heterogeneity and ≥75%, considerable heterogeneity †Inter-study variation adjusted (heterogeneous study removed from the pool of effect estimates). *Generated from adjusted total effect estimates from each n-3 PUFA random effect analysis; DPA: docosapentaenoic acid; DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid.

Table 2.2. Blood level omega-3 poly-unsaturated fatty acids vs. total prostate risk subgroup analysis model (prospective vs. retrospective)

Groups		Effect size and 95% interval			Test of null (2-Tail)		Heterogeneity^				Tau-squared			Publication bias	
Omega-3 derivatives	No. studies	Point Estimates	Lower Limit	Upper Limit	Z-value	P-value	Q-value	df	p-value	I²	Tau²	Standard Error	Variance	Begg	Egger
DPA	6	0.756	0.599	0.955	-2.347	0.019	3.883	5	0.566	0.000	0.000	0.060	0.004	1.000	0.540
Retrospective	2	0.620	0.278	1.382	-1.168	0.243	1.126	1	0.289	11.180	0.039	0.488	0.238		
Prospective	4	0.773	0.605	0.988	-2.055	0.040	2.433	3	0.488	0.000	0.000	0.055	0.003		
DHA	11	0.876	0.685	1.119	-1.059	0.290	18.991	10	0.040	47.343	0.072	0.073	0.005	0.436	0.239
Retrospective	6	0.769	0.558	1.060	-1.603	0.109	5.433	5	0.365	7.972	0.014	0.109	0.117		
Prospective	5	0.942	0.670	1.325	-0.342	0.733	11.213	4	0.024	64.327	0.094	0.107	0.011		
EPA	11	0.971	0.784	1.204	-0.264	0.792	14.741	10	0.142	32.162	0.039	0.056	0.003	0.533	0.671
Retrospective	6	0.851	0.634	1.143	-1.069	0.285	4.603	5	0.466	0.000	0.000	0.097	0.009		
Prospective	5	1.028	0.757	1.396	0.178	0.859	8.661	4	0.070	53.818	0.064	0.086	0.007		

DPA: docosapentaenoic acid; DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid.

Table 3. Blood level omega-3 polyunsaturated fatty acids vs. advanced prostate risk random effect analysis model

Groups		Effect size and 95% interval			Test of null (2-Tail)		Heterogeneity^				Tau-squared			Publication bias	
Omega-3 derivatives	No. studies	Point Estimates	Lower Limit	Upper Limit	Z-value	P-value	Q-value	df	p-value	I²	Tau²	Standard Error	Variance	Begg	Egger
DPA	3	0.870	0.514	1.473	-0.517	0.606	0.367	2	0.832	0.000	0.000	0.229	0.052	1.000	0.618
DHA	4	0.896	0.640	1.256	-0.637	0.524	2.289	3	0.515	0.000	0.000	0.102	0.010	1.000	0.342
EPA	4	0.975	0.582	1.634	-0.094	0.925	6.180	3	0.103	41.457	0.141	0.226	0.051	0.308	0.309
(DHA+DPA+EPA)*		0.908	0.708	1.164	-0.760	0.447	8.870	10	0.545	0.000	0.000	0.064	0.004		
(DHA+EPA)*		0.919	0.693	1.219	-0.585	0.559	8.482	7	0.292	17.471	0.027	0.081	0.007		

*Generated from total effect estimates from each n-3 PUFA random effect analysis; DPA: docosapentaenoic acid; DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid.

Table 4. Blood level omega-3 polyunsaturated fatty acids vs. high-grade prostate risk random effect analysis model

Groups		Effect size and 95% interval			Test of null (2-Tail)			Heterogeneity^			Tau-squared			Publication bias	
Omega-3 derivatives	No. of studies	Point estimates	Lower limit	Upper limit	Q-value	P-value	Z-value	p-value	df	I^2	Tau^2	Standard error	Variance	Begg	Egger
DPA	3	0.597	0.299	1.193	3.291	0.144	-1.460	0.193	2	39.231	0.149	0.381	0.145	1.000	0.930
DHA	5	1.233	0.769	1.978	8.593	0.385	0.869	0.072	4	53.449	0.154	0.205	0.042	0.221	0.051
DHA†	4	1.462	0.972	2.199	4.310	0.068	1.823	0.230	3	30.389	0.053	0.142	0.020	0.734	0.265
EPA	5	1.130	0.717	1.781	8.362	0.599	0.527	0.079	4	52.162	0.138	0.190	0.036	0.221	0.273
EPA†	4	1.317	0.910	1.908	3.931	0.145	1.458	0.269	3	23.675	0.034	0.117	0.014	0.734	0.952
(DHA+DPA+EPA)*		1.232	0.955	1.590	20.370	0.108	1.605	0.026	10	50.908	0.136	0.121	0.015		
(DHA+EPA)*		1.390	1.070	1.80	8.498	0.010	2.500	0.291	7	17.629	0.024	0.074	0.005		

^Inter-study heterogeneity was tested by Cochrane's Q (Chi²) at a significance level of P<0.10 and quantified by I², where I² ≥ 50 % is considered to be evidence of substantial heterogeneity and ≥75%, considerable heterogeneity; †Inter-study variation adjusted (heterogeneous study removed from the pool of effect estimates); *Generated from adjusted total effect estimates from each n-3 PUFA random effect analysis; DPA: docosapentaenoic acid; DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid.

Conclusion

This meta-analysis provided evidence to show that high blood level n-3 PUFA DPA is associated with reduced risk of prostate cancer. While high blood level of EPA and DHA in combination is associated with increase high-grade prostate tumour risk. These results must be interpreted with caution, since the etiology of prostate cancer is multifactorial and the metabolism of long chain n-3 PUFA in human body is complex.

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