



Fish Oil and Prostate Cancer Risk- Is there a link?

Several widely publicized clinical trials in the past weeks and months purport that the use of omega-3 fatty acids, especially those from supplemental fish oil, has no therapeutic value or are even potentially harmful to consume. This short communication is written to help put these reports within the context of the studies' own limitations and also the broader fish oil research that has gone virtually unreported during the same time.

Let's begin with the most recent study purporting to link fish oil with prostate cancer risk. The report was published online in the J. of the National Cancer Institute ([Online Abstract](#)) and soon afterward, headlines such as "*Men who take fish oil omega-3 supplements at 71% higher risk of prostate cancer: study*"¹ began floating around the internet, print and national television. One would assume by such headlines that this study was specifically designed to look at prostate cancer risk in men consuming fish oil supplements- it was not. In fact, this study didn't even look at fish oil (or even dietary fish) consumption in these subjects!

Instead, this report was a secondary analysis of data collected from the previously concluded SELECT (Selenium and Vitamin E Cancer Prevention Trial) trial, which recruited men over 50 with no history of prostate cancer who were then randomized to receive vitamin E, selenium, a combination of vitamin E plus selenium, or placebo and followed for prostate cancer incidence ([NCI's SELECT Website](#)). The data from this report is considered a case-cohort design, attempting to find an association between plasma phospholipid fatty acid levels in case subjects (those diagnosed with prostate cancer during the length of the trial) and compare those with study cohorts (similar subjects within the trial not diagnosed with prostate cancer during the length of the trial). It is important to note that the original vitamin E/selenium study was not designed to detect the association between plasma phospholipids and cancer risk and patients were not asked about their fish or fish oil supplement use at either the start or the length of the trial.

Nevertheless, they report that higher levels of 3 specific omega-3 fatty acids (EPA,DHA,DPA-combined) as a percent of plasma phospholipid fatty acids- were associated with a higher incidence of prostate cancer during the SELECT trial. While the authors are much more cautious in their direct indictment of omega-3 supplementation within their publication (since they have no data related to supplementation), one of the authors said in a press release "*We've shown once again that use of nutritional supplements may be harmful*" Here are a few reasons these conclusions and statements are unwarranted and misrepresent the data.

- The fatty acid levels reported here represent only a single blood draw taken at the start (baseline) of each participant's entry into the study, often years before a prostate cancer diagnosis was assigned to the subject. Since plasma phospholipid fatty acid content fluctuates with dietary intake on a day to day basis, a single time point may only reflect dietary habits within the previous week prior to the blood draw and may have no correlation to long-term omega-3 intake or blood levels.
- While the omega-3 fatty acid differences between groups were *statistically* different, they were not *clinically* significant. That is, the omega-3 levels reported would be considered "average" in all subject groups and the largest difference in the levels reported between groups could have been achieved with very low omega-3 consumption in a few weeks' time.(see endnote #2)²

- The authors admit that because of the high cost of phospholipid testing, that only case subjects diagnosed through 2007 (and their cohorts) were originally to be tested. But since “new finding” of associations between fatty acids and prostate cancer came to light- more subjects with high-grade cancer were analyzed in the 8th and 9th year of the trial. This highly unusual change in data set would have been disallowed in most other peer-review settings. The original data set was not published.
- In almost all cases of associative data, a number of variables are used to adjust the data. Typically these adjustments include most variables that might influence risk. While these data were adjusted for education, diabetes, family history of prostate cancer and the SELECT intervention assignment; these data were not adjusted for the most striking variables that affect risk in this population- age, race, BMI and PSA levels- information which may have nullified these statistical associations. How these reviewers ignored this most obvious adjustment and permitted the data to be reported without these adjustments is baffling.

Omega-3 associated with lower prostate cancer, breast cancer, CHD and total mortality.

Beyond the specific conclusion of this study is the broader epidemiological and scientific question of plausibility. The authors readily admit that there is no plausible scientific explanation for how long-chain fatty acids like EPA and DHA could actually cause prostate cancer. There is also the inconvenient fact that several people groups which consume high levels of omega-3 fatty acids and have plasma phospholipids much higher than the participants in this study have extremely low incidence of prostate cancer (i.e. Japan). More importantly, studies that specifically look at fish and fish oil consumption show a dramatic decrease in prostate cancer risk in older men, seeing a slightly higher risk associated only with salted and smoked fish intake.³ Other large meta-analysis have shown that even when overall prostate cancer incidence may be unaffected by omega-3 intake, prostate cancer *mortality* is dramatically lower in individuals with higher intake of marine omega-3 fatty acids.⁴

In fact, in a highly under-reported study published this year in the *Annals of Internal Medicine*, plasma phospholipid omega-3 fatty acids (much like the SELECT data above) were associated with lower total mortality- especially related to CHD deaths.⁵ However, in this study the plasma phospholipid fatty acid difference between the highest and lowest groups were highly clinically relevant (200-300% difference), as compared to the clinically irrelevant differences in the SELECT trial data (6% difference- see endnote #2).

Lost in all this has been another significant report published in the *British Medical Journal* which associates the intake of fish and marine omega-3 fatty acids with a reduced risk for breast cancer.⁶ This meta-analysis of 21 independent prospective cohort studies showed an overall 14% reduction in the relative risk for breast cancer related to marine omega-3 fatty acids. This risk reduction was associated with both the consumption of fish and fish oil, as well as tissue biomarker analysis (i.e. plasma phospholipids). They even suggested a “dose-response” relationship which suggested that the risk of breast cancer was reduced by 5% for each 100mg/day of marine omega-3 consumed.

Summary:

When the data from the subcohort of the SELECT trial is analyzed and placed alongside the growing epidemiological, interventional and mechanistic data (see below) - the purported relationship between consuming omega-3 fatty acids (in the diet or through dietary supplements) with an increased risk of prostate cancer cannot be supported. Furthermore, since this study did nothing to ascertain the consumption of fish or omega-3-containing supplements in these subjects, it makes the sensationalized media reports about this study even more disturbing. In addition, the fact that the association data was not adjusted for the most obvious factors (such as PSA levels, race, BMI and age) leaves us unsure that there

is any association at all; and leaves many others to suppose that strong bias may be at play here. We find it quite telling that one of the key authors of the trial is quoted in the DailyMail as saying ‘*There is not really a single example of where taking a supplement lowers chronic disease risk.*’⁷ On the contrary, we believe the current overall scientific evidence suggests that consumption of omega-3 fatty acids from fish oil supplements is not only safe at a wide-range of doses, but has proven efficacy in reducing risk for a wide-range of chronic conditions.

Recent animal or basic research on omega-3 fatty acids and prostate cancer

- Mechanisms of omega-3 polyunsaturated Fatty acids in prostate cancer prevention. [Biomed Res Int. 2013;2013:824563.](#)
- A low dietary ratio of omega-6 to omega-3 Fatty acids may delay progression of prostate cancer. [Nutr Cancer. 2013;65\(4\):556-62](#)
- 15-lipoxygenase metabolites of docosahexaenoic acid inhibit prostate cancer cell proliferation and survival. [PLoS One. 2012;7\(9\):e45480.](#)
- 22 : 6n-3 DHA inhibits differentiation of prostate fibroblasts into myofibroblasts and tumorigenesis. [Br J Nutr. 2012 Dec 28;108\(12\):2129-37](#)
- Effect of dietary polyunsaturated fatty acids on castration-resistant Pten-null prostate cancer. [Carcinogenesis. 2012 Feb;33\(2\):404-12.](#)
- Consumption of high ω-3 fatty acid diet suppressed prostate tumorigenesis in C3(1) Tag mice. [Carcinogenesis. 2012 Jan;33\(1\):140-8](#)
- Docosahexaenoic acid selectively induces human prostate cancer cell sensitivity to oxidative stress through modulation of NF-κB. [Prostate. 2011 Sep 15;71\(13\):1420-8.](#)

¹ <http://www.nydailynews.com/life-style/health/evidence-prostate-cancer-omega-3-link-article-1.1395853>

² For instance, the greatest difference between DHA levels in these subjects was reported as 0.18% (2.91% in the no cancer group and 3.09% in the high-grade cancer group, difference P=0.009). For comparison, other studies have shown that fish oil intake equivalent to *a single serving of fish per week* can raise DHA levels 0.63%, and do so in about 12 days. ([AJCN 2012; 96:748](#)). As Duffy MacKay, VP of Science & Regulatory Affairs at the Council for Responsible Nutrition said about the most recent study, these difference in omega-3 levels “*literally could have occurred if somebody ate a fish sandwich on their way to get their blood drawn*”

³ Consumption of Fish Products across the Lifespan and Prostate Cancer Risk [PLoS One. 2013; 8\(4\): e59799](#).

⁴ Fish consumption and prostate cancer risk: a review and meta-analysis. [Am J Clin Nutr. 2010 Nov;92\(5\):1223-33](#)

⁵ Plasma phospholipid long-chain ω-3 fatty acids and total and cause-specific mortality in older adults: a cohort study. [Ann Intern Med. 2013 Apr 2;158\(7\):515-25.](#)

⁶ Intake of fish and marine n-3 polyunsaturated fatty acids and risk of breast cancer: meta-analysis of data from 21 independent prospective cohort studies. [BMJ. 2013 Jun 27;346:f3706](#)

⁷ <http://www.dailymail.co.uk/health/article-2359466/Taking-omega-3-fish-oil-supplements-increase-risk-aggressive-prostate-cancer-70.html#ixzz2Z8s5FTyi>