ADVANCES

In EPA & DHA Research

Abstract Details

Background: Studies of dietary ω-3 fatty acid intake and prostate cancer risk are inconsistent; however, recent large prospective studies have found increased risk of prostate cancer among men with high blood concentrations of long-chain ω-3 polyunsaturated fatty acids ([LCω-3PUFA] 20:5ω3; 22:5ω3; 22:6ω3]. This case–cohort study examines associations between plasma phospholipid fatty acids and prostate cancer risk among participants in the Selenium and Vitamin E Cancer Prevention Trial.

Methods: Case subjects were 834 men diagnosed with prostate cancer, of which 156 had high-grade cancer. The sub-cohort consisted of 1393 men selected randomly at baseline and from within strata frequency matched to case subjects on age and race. Proportional hazards models estimated hazard ratios (HR) and 95% confidence intervals (CI) for associations between fatty acids and prostate cancer risk overall and by grade. All statistical tests were two-sided.

Results: Compared with men in the lowest quartiles of LCω-3PUFA, men in the highest quartile had increased risks for low-grade (HR = 1.44, 95% CI = 1.08 to 1.93), high-grade (HR = 1.71, 95% CI = 1.00 to 2.94), and total prostate cancer (HR = 1.43, 95% CI = 1.09 to 1.88). Associations were similar for individual long-chain ω-3 fatty acids. Higher linoleic acid (ω-6) was associated with reduced risks of low-grade (HR = 0.75, 95% CI = 0.56 to 0.99) and total prostate cancer (HR = 0.77, 95% CI = 0.59 to 1.01); however, there was no dose response.

Conclusions: This study confirms previous reports of increased prostate cancer risk among men with high blood concentrations of LCω-3PUFA. The consistency of these findings suggests that these

Omega-3s and Prostate Cancer Risk

Review of:

"Plasma Phospholipid Fatty Acids and Prostate Cancer Risk in the SELECT Trial" Theodore M. Brasky, Amy K. Darke, Xiaoling Song, Catherine M. Tangen, Phyllis J. Goodman, Ian M. Thompson, Frank L. Meyskens Jr, Gary E. Goodman, Lori M. Minasian, Howard L. Parnes, Eric A. Klein, Alan R. Kristal

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GOED Comment on Experimental Design and Results

The test cohort was the same as used for the abandoned SELECT trial (Selenium and Vitamin E Cancer Prevention Trial) enlisting men over the age of 55 from the USA, Canada and Puerto Rico from 2001 to 2004. The cohort was relatively healthy and intelligent in relation to the general population. Fatty acids were analyzed from a single blood serum sample taken on enlistment. The absolute individual fatty acids were not reported; rather they were expressed as % of total fatty acids.

The study used a case-cohort design nested with the SELECT cohort. Cases of prostate cancer were reported as low or high grade according to defined clinical parameters.

The incidence of prostate cancers in relation to individual blood serum fatty acids was assessed by estimating hazard ratios using a Cox proportional hazard (CPH) statistical model. In such models, the covariate is multiplicative with respect to the hazard rate. This model assumes a linear response with time elapsed.

fatty acids are involved in prostate tumorigenesis. Recommendations to increase LCω-3PUFA intake should consider its potential risks.

Only total omega-3 PUFA (EPA +DHA +DPAn-3) gave a statistically significant association (p< 0.05). The hazard ratios (95% CI) are given in the table below:

Omega 3% of FA	Low grade prostate cases(n)	Hazard ratio for Low grade	High grade prostate cases(n)	Hazard ratio for High grade
<3.68	146	1	26	1
3.68-4.41	159	1.1	35	1.39
4.42-5.31	176	1.26	52	1.87
>5.31	203	1.44	43	1.71

Using the CPH model and assuming a 50% increase in risk with time, the authors suggest that omega-3 PUFA's are associated with a 22-25% prostate cancer risk.

GOED Takeaways

While any recommendation for supplementation should consider any associated risks, we believe the authors' conclusion is irresponsible and blatantly ignores the totality of the scientific evidence that has been collected over multiple decades regarding the health benefits of marine omega-3 fatty acids.

- This study was *not* specifically designed to look at the exact relationship between omega-3 fatty acid intake and prostate cancer.
- The difference in mean blood plasma phospholipid fatty acids blood level for omega-3s was 4.66% in the combined cancer group versus 4.48% in the control. They are basing their results on just ca. 0.2% difference in omega-3 levels.
- If the findings were true, then prostate cancer would be rampant in any country with high seafood consumption (Scandinavia, Japan etc) and conversely, low level consumption should be protective. Clearly this is not the case.
- Plasma phospholipid fatty acids as measured in this study are not a good index of long term intake and are influenced dramatically by a single meal, or even timing of a fish oil dose. A single fish oil dose massively increases LC omega 3 (typically increasing levels by 100% or more) in about 4-12 hours and then washes out around 48 hours.
- Absolute serum levels of EPA, DHA, DPAn-3 were not reported.
- No documentation was provided in the paper regarding intake of fish or fish oil in the study group.
- The study was not designed to look at omega-3 and confounded with selenium and Vitamin E used in the treatment arms.
- It is very possible the statistical model used (Cox proportional hazards) was not appropriate for this study. This model is suitable for a drug taken at the same time every day or exposure to a toxin throughout the day at the same level, but not for something like fish or fish oil intake where the levels in blood serum will vary considerably depending on food and supplement consumption patterns.
- The association between individual omega-3 fatty acids, EPA, DPA and DHA and prostate cancer was NOT statistically significant within the CPH model.
- The DPA:high grade data violated the CPH model assumptions (as did 3 other fatty acids associations).

- The so called "meta-analysis" of earlier studies carried out at the end of the paper actually only included three previous studies, one of which was his own (Brasky, 2011). Another by Park et al. (2009) used the same nested case control design, while the remaining study by Chavarro et al (2007) showed a strong benefit for marine omega 3 fatty acids *reducing the risk* of prostate cancer.
- In a similar study two years ago, the same lead author (Brasky, 2011) used the same methodology, though a different cohort, to attempt to find a link between omega-3's and prostate cancer. In this case, no association with EPA was found, and though a real association with DHA was found, it was not linear with time/dose dependent and applied to high grade tumors only. The actual mean DHA levels, reported as a % of total serum fatty acids, for the control group, low grade prostate cancer group and high grade prostate cancer group respectively were 2.84, 2.89, 2.99 – an *absolutely minimal real difference.*
- The test cohort included sick and healthy people. It is possible that sick people were taking fish oil supplements at a higher rate than the healthy individuals.

What Else Should You Know?

- A recent meta-analysis of fish consumption and prostate cancer by Szymanski et al. (2010) reported a large reduction in late stage or fatal prostate cancer among cohort studies.
- Several population based studies have shown a benefit of increased omega-3 fatty acid intakes to reducing prostate cancer risk (Lietzman et al., 2004, Terry et al., 2001).
- A recent meta-analysis by Zheng (2013) of 16 independent cohort studies reported the association between marine n-3 PUFA (reported as intake or biomarker data) and risk of breast cancer, involving 16,178 breast cancer events and 527,392 participants. Marine n-3 PUFA was significantly inversely associated with risk (relative risk 0.86, 95% confidence interval 0.78 to 0.94). Dose-response analysis indicated that a 0.1g/day increment of dietary marine n-3 PUFA was associated with 5% lower risk of breast cancer.

Suggested Citation

Global Organization for EPA and DHA Omega-3s (2013). Omega-3s and Prostate Cancer Risk [Peer commentary on the paper "Plasma Phospholipid Fatty Acids and Prostate Cancer Risk in the SELECT Trial" by Brasky T.M. et al, 2013, JNCI, doi:10.1093/jnci/djt174.].

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