IADSA SCIENTIFIC REPONSE - IADSA SCIENTIFIC ALERT SERVICE

Publication: Journal of the National Cancer Institute
Title: Plasma phospholipid fatty acids and prostate cancer risk in the SELECT trial
Authors: Brasky TM, Darke AK, Song X, Tangen CM, Goodman PJ, Thompson IM, Meyskens FL Jr, Goodman GE, Minasian LM, Parnes HL, Klein EA, Kristal AR
Date: July 10 2013

SUMMARY OF THE STUDY:

Objective: In view of inconsistent data on blood concentrations of long chain omega-3 polyunsaturated fatty acids (PUFA) and prostate cancer risk, data from the selenium and vitamin E cancer prevention trial (SELECT)[1,2] were used as an additional resource to examine any association between plasma phospholipid fatty acids and prostate cancer risk.

Design: A prospective, case-cohort study nested within SELECT (a randomised, placebo-controlled trial that tested whether selenium and vitamin E alone or in combination, reduced prostate cancer risk.) Cases were men with blood samples taken at baseline (between 2001 and 2004) and later diagnosed with primary prostate cancers. Controls were matched by age and race at the time of diagnosis. Overall, the study compared 834 cases diagnosed before 2007, of which 684 were diagnosed with low grade cancer, 69 for whom grade was not available, and 156 cases of high grade cancer (including an additional 75 high grade cases diagnosed before July 31 2009), plus 1393 controls.

Main Outcome Measures: Plasma phospholipid concentrations of omega-3, omega-6 and trans fatty acids, and risk of total, low-grade and high-grade prostate cancer.

Results: Compared with the lowest quartile of total long-chain omega-3 PUFA, the highest quartile with low-grade prostate cancer had a 44% increased risk (95% CI = 8% to 93%), for high-grade prostate cancer there was a 71% increased risk (95% CI = 0% to 194% and hence not statistically significant), and for all grades of prostate cancer there was an 43% (95% CI = 9% to 88%) increased risk. Each 50% increase in total long-chain omega-3 PUFA was associated with a 23% to 24% increased prostate cancer risk.

For docosapentaenoic acid (DPA) the corresponding risks were statistically significant, being 56% for low-grade prostate cancer, 15% for high-grade and 38% for all grades of prostate cancer. Each 50% increase was associated with a 23% to 30% increased risk.

For EPA the corresponding risks were not statistically significant.

For DHA the corresponding risks were statistically significant for low-grade prostate cancer (42% increased risk), and for all grades of prostate cancer (39% increased risk), but were not significant for high-grade prostate cancer. Each 50% increase was associated with a 21 to 26% increased risk.

For low-grade prostate cancer, higher concentration of linoleic acid was associated with a 25% reduced risk (95% CI = 1% to 44%), but the associations were not significant for high-grade and total prostate cancer. Also, there was no dose response.

For *trans* fatty acids there was weak evidence that higher TFA 16:1 was associated with increased risk, based on statistically significant or borderline significant trends across quartiles of exposure.

The authors also conducted a meta-analysis of studies reporting associations between EPA or DHA and prostate cancer risk. They reported that of four large, recent studies, three support a positive association between omega-3 fatty acids and increased risk of prostate cancer, though with inconsistences regarding cancer grade and specific omega-3 fatty acids and one study reported inverse associations.[3]

Authors identified strengths of the study: A prospective study based on a large number of prostate cancer cases.

Authors identified limitations of the study: Expressing fatty acids as weight proportions could create spurious results because an increase in the percentage of one type of fatty acids results in a decrease in the others (however omega-3 fatty acids are present in very low concentrations). These is also an inverse association of omega-3 with omega-6 fatty acids.

Authors conclusions: The replication of previously reported findings in this new analysis suggests a potential role for long-chain omega-3 PUFA in prostate cancer. Though long-chain omega-3 PUFA have been associated with reduced risk of cancer and heart disease, the authors cite a meta-analysis published in 2012[4] that reported no association of long chain omega-3 PUFA on all-cause mortality, cardiac death, heart attack or stroke. Hence the authors conclude that the potential risk of increasing long-chain omega-3 PUFA intake should be taken into consideration.

EXPERT RESPONSES:

The SELECT study was not designed to investigate the role of omega-3 fatty acid intake on prostate cancer. In contrast, it was designed to investigate the effects of selenium and vitamin E on prostate cancer prevention.

There is no data in the study on dietary intakes of fish oils or oily fish consumption, or to support ingestion of omega-3 supplements. Hence no firm conclusions can be drawn with regard to omega-3 fatty acid intake and prostate cancer risk.

Evidence from a prospective, case-control study can only indicate a potential association. It does not demonstrate cause and effect, and hence it cannot be concluded that omega-3 fatty acids have a causative role in the development of prostate cancer.

The mean concentrations of plasma phospholipids were very similar between the cases and controls i.e. 4.48 (4.41 to 4.55) in the controls and 4.66 (4.56 to 4.75) in the total cases.

Plasma phospholipid fatty acids were used as the index of omega-3 fatty acid status. This endpoint is highly influenced by recent intake, e.g. the last meal or timing of ingestion of a fish oil supplement, and hence do not reflect longer-term status. Concentrations in red blood cells would have been a preferred measure.

Though the authors report consistency with previous findings, a similar study by the same first author previously reported[5] found that no fatty acids were associated with low-grade prostate cancer risk, and DHA was positively associated with high-grade disease (quartile 4 vs. 1: odds ratio (OR) = 2.50, 95% confidence interval (CI): 1.34, 4.65). The current results do not replicate these findings.

There is no proposed, coherent mechanism for the effect. In contrast, inflammation plays a role in the aetiology of many cancers and the long-chain omega-3 fatty acids show anti-inflammatory effects.

Regarding the new meta-analysis reported in the paper, it is not clear how the studies were selected and particularly whether this was based on a systematic review of the literature. The selection of studies reporting associations could be subject to publication bias.

Other studies and meta-analyses have shown benefits of increased omega-3 fatty acid intake and reduced risk of prostate cancer.[6,7,8]

In Europe, a recent scientific opinion was published on upper safe levels of long chain omega-3 fatty acids.[9] It was concluded that supplemental intakes of EPA and DHA combined at doses up to 5 g/day, and supplemental intakes of EPA alone up to 1.8 g/day, do not raise safety concerns for adults, and that supplemental intakes of DHA alone up to about 1 g/day do not raise safety concerns for the general population.

Also in Europe, following a rigorous assessment process, DHA and EPA have been awarded authorised health claims for heart health benefits. These include for contribution to the normal function of the heart, for the maintenance of normal blood pressure, and for the maintenance of normal blood triglyceride levels.[10]

In America, the American Heart Association, the U.S. Institute of Medicine's Food Nutrition Board (IOM FNB) and the 2010 Dietary Guidelines all have current policies advising Americans to eat more oily fish because of the beneficial effects of omega-3 fatty acids.

In addition, the World Health Organization found convincing evidence for reduced risk of cardiovascular disease and consumption of fish oils (eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).[11]

Overall, this supports evidence of the benefits of omega-3 fatty acids, and of their safety.

References:

1. Lippman SM, Goodman PJ, Klein EA, Parnes HL, Thompson IM, Jr., Kristal AR, et al. Designing the Selenium and Vitamin E Cancer Prevention Trial (SELECT). J Natl Cancer Inst. 2005 Jan 19;97(2):94-102.
2. Lippman SM, Klein EA, Goodman PJ, Lucia MS, Thompson IM, Ford LG, et al. Effect of selenium and vitamin E on risk of prostate cancer and other cancers: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). JAMA. 2009 Jan 7;301(1):39-51.
3. Chavarro JE, Stampfer MJ, Li H, Campos H, Kurth T, Ma J. A prospective study of polyunsaturated fatty acid levels in blood and prostate cancer risk. Cancer Epidemiol Biomarkers Prev. 2007 Jul;16(7):1364-70.
4. Rizos EC, Ntzani EE, Bika E, Kostapanos MS, Elisaf MS. Association between omega-3 fatty acid supplementation and risk of major cardiovascular disease events: a systematic review and meta-analysis. JAMA. 2012 Sep 12;308(10):1024-33.
5. Brasky TM, Till C, White E, Neuhouser ML, Song X, Goodman P, et al. Serum phospholipid fatty acids and prostate cancer risk: results from the prostate cancer prevention trial. Am J Epidemiol. 2011 Jun 15;173(12):1429-39.
6. Leitzmann MF, Stampfer MJ, Michaud DS, Augustsson K, Colditz GC, Willett WC, et al. Dietary intake of n-3 and n-6 fatty acids and the risk of prostate cancer. Am J Clin Nutr. 2004 Jul;80(1):204-16.
7. Szymanski KM, Wheeler DC, Mucci LA. Fish consumption and prostate cancer risk: a review and meta-analysis. Am J Clin Nutr. 2010 Nov;92(5):1223-33.
8. Terry P, Lichtenstein P, Feychting M, Ahlbom A, Wolk A. Fatty fish consumption and risk of prostate cancer. Lancet. 2001 Jun 2;357(9270):1764-6.
9. EFSA 2012. Scientific opinion on the tolerable upper intake levels of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) and docosapentaenoic acid (DPA). EFSA Journal 10 (7): 2815.
10. European Union (2011). "EU register on nutrition and health claims." www.ec.europa.eu/nuhclaims.
11. WHO/FAO Expert Consultation (2003). Diet, nutrition and the prevention of chronic diseases. Geneva, World Health Organisation.

12th July 2013