7/18/2013: This whole thing seems fishy!

Here are the headlines......

“Omega-3 supplements linked to prostate cancer” – Fox News
“Hold the salmon: Omega 3 fatty acids linked to higher risk of cancer” – CNN

Abstract details:

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

**Conclusions:** This study confirms previous reports of increased prostate cancer risk among men with high blood concentrations of LC 3PUFA. The consistency of these findings suggests that these fatty acids are involved in prostate tumor genesis. Recommendations to increase LC 3PUFA intake should consider its potential risks.


This article certainly merits attention because it challenges our longstanding recommendations to eat a healthy Mediterranean diet rich in Omega 3 nutrients and low in saturated fats. Additionally, in some cases, we utilize Omega-3 supplementation to treat vascular inflammation (OCEAN trial), plaque stabilization (COMBOS) and prevention of vascular events and death (JELIS and GISSI).

This research (Brasky et al), is challenging from several vantage points – statistically, methodologically and intuitively. When determining whether or not Omega-3 supplementation or a diet that contains fish intake is healthy and safe, we must challenge the rigors of this research from every angle. This list is NOT meant to be conclusive but certainly raises points of concern.
Methodologically –
1. This is an observational trial – NO cause/effect was reported.
2. We do not know how many of the men in this trial had prostate cancer BEFORE the trial was initiated. Prostate cancer is a very slow growing cancer therefore there is no way of knowing if they had early cancer prior to entering into the trial.
3. This was NOT a trial to test supplement intake – no supplements or dietary intake were evaluated. Plasma phospholipid fatty acids (measured in this study) can be influenced by a fish meal or Omega-3 dose intake....no controls for Omega 3 intake were offered.
4. No documentation was provided regarding intake of fish or Omega-3 supplements were recorded in the trial.
5. Absolute levels of EPA, CHA, DPAn-3 were not reported.

Statistically –
1. The difference in mean blood plasma phospholipid fatty acids blood level for omega-3 was 4.66% in the cancer group vs 4.48% in the non-cancer case matched group. The association between Omega-3 and prostate cancer is being based on a 0.2% difference in Omega-3 levels. Some experts have commented that the levels in both groups are well below what would be expected with supplemental omega-3.
2. Co-founders for prostate cancer were not controlled in this observational study – this data also demonstrated that the prostate cancer positive subjects were smokers (53%), regularly consumed alcohol (64%), had a first degree relative with prostate cancer (30%), and were obese (80%). These confounding variables were not controlled for in the study.
3. When associations are made into conclusions false assumptions can be made. For example, this observational research also stated that participants with the highest levels of trans fats in their blood also had the lowest risk for prostate cancer. Historical data would lean away from consuming diets high in trans fats (donuts, French fries) as a way to prevent any type of cancer. There was also a strong correlation of risk with education. People with higher levels of education had higher risk of prostate cancer. We certainly would not take that to mean advising boys to drop out of school after 8th grade to reduce prostate cancer risk!
4. In 2010, there were 28,500 prostate cancer related deaths as opposed to 207,500 deaths from ischemic heart disease (7-fold difference).
5. If we chose to believe this possible association as a cause and effect relationship, taking omega 3 fatty acid would increase the risk of prostate cancer by 50%. A conservative conclusion from previous data suggests that Omega-3’s reduce ischemic heart disease by 10%. So, weighing the benefit vs risk, taking Omega-3 fatty acids would increase annual prostate CA deaths to 42,750 and decrease annual IHD deaths to 186,750. That individual is still 4.5 times more likely to die of heart disease than prostate cancer.
Intuitively –

1. If Omega 3 fatty acid increased prostate cancer, countries with high fish intake would likely show an increase prostate cancer incidence. This does not appear to be the case. Example: Alaska Eskimos compared to US Whites (followed for 15 years from 1969-1983) had lower risk of prostate cancer despite a diet rich in Omega-3's (Artic Chard and Artic Cod and Trout).

2. Likewise, if this premise was true, prostate cancer would be higher in countries where fish intake was low and this has never been proven.

3. Many studies conflict with this data –
   a. Zheng (2013) – meta analysis with 16 cohort studies showing that an intake of Omega-3 had a dose-related inverse relationship with risk of breast cancer.
   b. Szymanski (2010) – meta analysis demonstrating that fish consumption had a reduction in late stage or fatal prostate cancer among cohort studies.
   c. Lietzman (2004), Terry (2001) – population based studies showing increased Omega 3 fatty acid intake and reduction of prostate cancer.

Conclusion:
Omega-3 fatty acid intake is sometimes a necessary component to the treatment regimen for atherosclerotic stabilization and vascular inflammation. Each recommendation must be determined on an individual basis – there is no panacea treatment nor is there a miracle cure for vascular disease. If Omega-3 is necessary, whether it be through diet or supplementation, the risk versus benefit must be discussed individually. Based on this latest observational research, a conclusion regarding cause and effect is unable to be established. For now, we must rely on the National Cancer Institute’s publications regarding the leading risk factors for prostate cancer remain: Age (>65 years old), Race (African American highest risk), Family History, Obesity, Smoking, Sedentary Lifestyle, and a diet high in Saturated Fat (*which is in direct converse to this most recent observational research). At best, this latest publication should stimulate a long term randomized double blind study to examine possible cause and effect.

-Amy Doneen MSN ARNP
-Bradley Bale MD
References:


Yokoyama, M., Origasa, H., Matsuzaki, M., Matsuzawa, Y., Saito, Y., Ishikawa, Y., ... Shirato, K. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. The Lancet, 369(9567), 1090-1098. doi: http://dx.doi.org/10.1016/S0140-6736(07)60527-3