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Omega-3 and Prostate Cancer Risk: Much Ado About Nothing

Recently there has been a lot of media coverage about the article **Brasky et al. Plasma Phospholipid Fatty Acids and Prostate Cancer Risk in the SELECT Trial. JNCI July 10, 2013** claiming that higher levels of omega-3 fatty acids in the blood increase the risk of prostate cancer.

I have critiqued the paper and, as you will see, discovered it to be scientifically invalid in terms of both its methodology and conclusions.

Let's take some time now to go through the paper itself and the larger issue of omega-3 and prostate health.

The SELECT trial was actually a trial designed to study the effects of selenium and Vitamin E supplementation on Prostate Cancer risk. The study was never designed or set up to prospectively study either the intake of fish or fish oil or to measure the effect of fish or fish oil consumption on the incidence of prostate cancer.

They did not regulate or control the consumption of fish or fish oil, they did not even measure or record the consumption of fish or fish oil. They did not conduct before and after measurements of omega-3 levels in any of their subjects.

The data these authors used was from a group of people with diagnosed prostate cancer who were then compared to retrospectively chosen age-matched subjects from the trial who did not have prostate cancer. **NO CAUSE AND EFFECT RELATIONSHIP, UNDER ANY CIRCUMSTANCE, CAN BE CLAIMED FROM THIS TYPE OF DATA.**

What they did, after all the data had been collected not before (meaning retrospectively not prospectively), was select those subjects who developed prostate cancer and then measure their omega-3 levels. As they did not design a study to measure omega-3 levels they had nobody to compare these people to so they randomly selected age-matched controls from the subject pool who did not have prostate cancer. This is completely invalid. There is no possible way to determine any cause and effect relationship from such methodology and to suggest their findings do so is both unscientific and unethical. It is the stuff of media headlines not scientific research.

So of the 35,533 male subjects over the age of 50 in the trial they selected the 834 who actually developed cancer (that is one out of every 42 subjects; that is 2.4% of the men in the trial that developed cancer or 2.4 out of every 100 men).

They then took those retrospectively selected 824 subjects and compared their omega-3 levels to 1364 age-matched subjects selected from the study that did not have cancer. They did not look at the omega-3 fatty acid levels of ALL 35,533 subjects and see if there was a trend toward higher omega-3 levels and cancer, they instead took those with cancer and then compared their omega-3 levels with a very small selected sample of those without cancer. Are you kidding me?? We have absolutely no idea, and neither do they, of

the omega-3 levels of the over 33,000 subjects who did not develop cancer!

Even worse their conclusion starts with the statement, "In this large, prospective trial, high plasma phospholipid concentrations of long-chain n-3 PUFA were associated with statistically significant increases in prostate cancer risk."

This is SO MISLEADING! The actual study on selenium and vitamin E was prospective but the data they got for the omega-3 was all collected retrospectively as part of a case-cohort study of the subjects that had already been a part of the SELECT study. The data on omega-3 and prostate cancer was NOT from a prospective trial at all and none of the variables were controlled!

But that is not the most disturbing part. If you look at the raw data what you will find out is that the selected 1364 subjects without cancer had a mean omega-3 fatty acid percentage of 4.48% of total fatty acids, the subjects that developed low grade cancer had a mean omega-3 fatty acid percentage of 4.66%, and the subjects that developed high grade cancer had a mean omega-3 fatty acid percentage of 4.71%. This means the absolute difference in fatty acid level was 0.18 % between the no cancer and low grade cancer group and 0.23% between the no cancer and high grade cancer group. This is less than a quarter of one percent. The physiological and/or clinical significance of this is not even calculable. The difference this represents in daily consumption would be negligible at best. Most experts agree that omega-3 fatty acids should make up much more than 5% in HEALTHY subjects so these subjects with and without cancer were deficient in omega-3 fatty acids!

Worse we cannot compare groups of people at all. We can only compare the few individuals with cancer to a selected few age-matched controls because they did not have two groups! We don't even know what the omega-3 fatty acid levels were of the over 33,000 subjects in the study who did not develop cancer. We have to assume that the 1364 subjects they chose as controls represent the other 33,000 subjects without cancer. This is so ridiculous it is hard to imagine it got published. Of course they don't explain it this way in the study; they just use a bunch of statistical jargon to impress the readers, most of whom will never realize what actually went on here.

Remember also that we have no data about how much omega-3 fatty acids these subjects were consuming or what their source of omega-3 fatty acids were (contaminated fish with cancer causing mercury and PCBs or contaminant-free fish oil).

VERY IMPORTANTLY, a study out of Norway showed that fish oil consumption was protective but that raising omega-3 levels with the consumption of salted or smoked fish was associated with a 200% increase of advanced prostate cancer both in early and later life.

"High intake of salted or smoked fish was associated with a 2-fold increased risk of advanced prostate cancer both in early life and in later life. Men consuming fish oil in later life had a lower risk of advanced prostate cancer." Torfadottier et al. Consumption of fish products across the lifespan and prostate cancer risk. April 17, 2013 PLOS

***Innate Choice Omega Sufficiency is filtered and then third party tested to be proven to be free of the contaminants found in salted or smoked fish.**

"Environmental factors and sources of fish oil have also been reported to contribute to prostate cancer development. Two studies have reported that environmental toxins such as polychlorinated biphenyls or methylmercury compounds, which are found in

contaminated marine fish, when consumed in the diet, can disrupt androgen and estrogen balance that may be associated with prostate cancer development." (Sorongon-Legaspi et al. Blood level omega-3 fatty acids as risk determinant molecular biomarker for prostate cancer. Prostate Cancer Volume 2013 Article ID 875615)

***Innate Choice Omega Sufficiency is filtered and then third party tested to be proven to be free of such contaminants.**

We not only don't know if they were taking fish oil supplements we don't know which type of fish oil supplement they were taking if they were taking them. This is also important because many fish oils are concentrates and don't contain all the naturally occurring fatty acids like DPA and other cofactors which can make a significant difference.

"Notably, there was a significant **negative association** between high levels of blood DPA level and prostate cancer risk with no significant heterogeneity, interstudy variability, or publication bias, which suggests that this long-chain n-3 PUFA may decrease the risk of prostate cancer development. DPA is abundant in whale meat, seal oil, and marine fatty fish, although in smaller quantities than EPA and DHA, in combination with which it is usually found." (Sorongon-Legaspi et al. Blood level omega-3 fatty acids as risk determinant molecular biomarker for prostate cancer. Prostate Cancer Volume 2013 Article ID 875615)

***Innate Choice Omega Sufficiency is NOT a concentrate and thus contains all the naturally occurring fatty acids, including DPA.**

We also know that in this trial many of the subjects were given synthetic vitamin E (many more may have been taking other synthetic vitamins) which have already been shown to increase the incidence of cancer and death.

Importantly in this study they admit that, "In 2011, after an additional 54,464 person-years of follow up, we reported that vitamin E (synthetic), in contrast with a placebo, increased prostate cancer risk by 17%."

This is not the only study to show detrimental effects of supplementing with RDA amounts of synthetic vitamins. The Alpha-Tocopherol Beta Carotene (ATBC) Trial showed a higher mortality rate in the synthetic beta-carotene group and no benefit from the alpha-tocopherol group. (Blumberg, J and Block, G. The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study in Finland. Nutr Rev. 1994; 52 (7): 242-245).

The Heart Outcomes Prevention and Evaluation (HOPE) study reported greater all-cause mortality with synthetic vitamin E (tocopherol) supplementation. (Yusuf, S. et al. Vitamin E supplementation and cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. N Engl J Med. 2000 342(3) : 154-160).

***Innate Choice Vita Sufficiency (available in August 2013) does NOT contain any synthetic vitamins and is the only vitamin/mineral supplement made from 100% certified organic plants and algae.**

It is also important to put all this in perspective with the fact that several properly designed prospective studies have found that omega-3 consumption reduces either the risk of development of prostate cancer or the rate of mortality for those diagnosed with prostate cancer.

"In a recent population-based prospective cohort study of 90,296 Japanese subjects, Sawada et al. reported that consumption of n-3-rich fish or n-3 PUFA, particularly EPA,

DPA, and DHA, appears to protect against the development of hepatocellular carcinoma (HCC). In another population-based prospective study in Japan, there was an inverse relationship between marine n-3 PUFA intake and the risk of colorectal cancer, but this association was only statistically significant in the proximal site of the large bowel." (Gu et al. **Mechanisms of Omega-3 polyunsaturated fatty acids in prostate cancer prevention. Biomed Res Int v.2013 May 2013**)

"We found that men with high consumption of fish had a lower risk of prostate cancer, especially for metastatic cancer." (Augustsson et al. **A prospective study of intake of fish and marine fatty acids and prostate cancer. Cancer Epidemiol Biomarkers Prev 2003 Jan; 12 (1): 64-7**)

***Innate Choice Omega Sufficiency is NOT a concentrate and thus contains all the naturally occurring fatty acids and thus most closely reflects the consumption of fish.**

"We studied the association between fish consumption and prostate cancer in a population-based prospective cohort of 6272 Swedish men. During 30 years of follow up, men who ate no fish had a two-fold to three-fold higher frequency of prostate cancer than those who ate moderate or high amounts did." (Terry, et al. **Fatty fish consumption and risk of prostate cancer. Lancet 2001 June 2, 357 (9270): 1764-6**)

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"During 382,144 person-years of follow up, 2161 men were diagnosed with prostate cancer and 230 died of prostate cancer. Fish intake was unrelated to prostate cancer incidence. Survival analysis among the men diagnosed with prostate cancer revealed that among those consuming fish >5 times/wk had a 48% lower risk of prostate cancer death than did men consuming fish less than once weekly. These results suggest that fish intake is unrelated to prostate cancer incidence but may improve prostate cancer survival. (Chavarro et al. **A 22-y prospective study of fish intake in relation to prostate cancer incidence and mortality. Am J Clin Nutr 2008 Nov;88(5):1297-303**)

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"Our analyses provide no strong association of a protective association of fish consumption with prostate cancer incidence but showed a significant 63% reduction in prostate cancer-specific mortality." (Szymanski, et al. **Fish consumption and prostate cancer risk: a review and meta analysis. Am J Clin Nutr. 2010, 92(5): 1223-33**)

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There is also a lot of basic science research data to explain why sufficient intake of omega-3 fatty acids could prevent cancer and increase survival of those with cancer. It is an essential nutrient!

One of the best articles I have seen explaining the physiological role (and importance) of omega-3 essential fatty acids is 'Mechanisms of Omega-3 Polyunsaturated Fatty Acids in Prostate Cancer Prevention' by Gu et al. published in the journal **Biomedical Research International** in May 2013. Here are some quotes:

"The health benefits of omega-3 polyunsaturated fatty acids (n-3 PUFA), mainly eicosapentaenoic acid (EPA 20:5) and docosahexaenoic acid (DHA, 22:6), have been long

known."

"Many new discoveries have advanced our understanding about the activities of n-3 PUFA against human disease. For example, DHA-receptor GPR120 has been demonstrated to play a role in sensing and controlling obesity and metabolic syndrome; the recently identified omega-3 mediators, resolvins, and protectins have been demonstrated to have anti-inflammatory and proresolving activities."

"Hu et al. reported that n-3 PUFA-induced apoptosis in human prostate cancer cells occurs through upregulation of syndecan-1 (SDC-1) expression followed by concomitant suppression of PDPK1/AKT/BAD phosphorylation. n-3 fatty acids may also decrease cell proliferation and induce apoptotic cell death in human cancer cells by decreasing signal transduction through the AKT/NFκB cell survival pathway and by modulating the PI3K/AKT/p38 MAPK pathway."

"Using prostate-specific Pten knockout mice, an immune-competent, orthotopic prostate cancer model, and diets with defined PUFA levels, we found that n-3 fatty acid reduced prostate tumor growth, slowed histopathological progression, and increased survival, whereas n-6 fatty acid had opposite effects."

"Using a prostate-specific Pten knockout mouse prostate cancer model, we showed that a ratio of n-6 to n-3 **below 5** was effective in slowing cancer progression. Brown et al. reported that AA might potentiate the risk of metastatic prostate cancer cell migration and seeding at the secondary site *in vivo*, and lowering the n-6/n-3 ratio in diet by uptake of n-3 PUFA might reduce this risk."

The omega 6/3 ratio in the blood samples of all the subjects retrospectively chosen from the SELECT trial and used to claim that higher omega-3 levels caused prostate cancer was over 6! These subjects were ALL DEFICIENT in omega 3 fatty acids and had levels far too low for any benefit!

What about the actual physiological plausibility of omega-3 fatty acids causing prostate cancer? Well the authors of the SELECT study fail to offer any plausible physiological explanation for their results.

"Long-chain ω-3 PUFA have many physiological effects. They are considered anti-inflammatory because of their multiple effects on inflammation pathways, such as inhibition of tumor necrosis factor alpha and modification of eicosanoid activity, and they also affect cell permeability, gene expression, and signal transduction. **It is unclear why high levels of long-chain ω-3 PUFA would increase prostate cancer risk**, and further study will be needed to understand the mechanisms underlying the findings reported here."

The fact of the matter is that their data does NOT provide any evidence that omega-3 fatty acids do increase prostate cancer risk. The scientific fact is that no valid scientific study has ever provided data to show a causal relationship between omega-3 fatty acids and an increased risk of prostate cancer or any other kind of cancer. I strongly suggest that this is why the physiological relationship is so unclear! Further, the subjects in this study did NOT have high levels of long-chain omega-3 fatty acids; they had dangerously low levels.

In the words of more responsible authors, "Cautious interpretation of these results must be done, since prostate carcinogenesis is multifactorial, and the body's metabolism of n-3 PUFA is complex." (Sorongon-Legaspi et al. **Blood level omega-3 fatty acids as risk determinant molecular biomarker for prostate cancer. Prostate Cancer Volume 2013 Article ID 875615**)

It is ridiculous and irresponsible to conclude from the SELECT study that omega-3 fatty acids are the factor that caused prostate cancer. Now, if other **prospective controlled trial** evidence showed an increase of cancer with an increased intake of omega 3 fatty acids I could understand the suggestion but this is simply not the case. What we have here is correlation being disguised as cause and effect.

An example would be studying drowning victims and then comparing them to randomly chosen subjects who did not drown and measuring sugar levels in the blood. You would likely find that those who drown had a higher level of sugar in the blood compared to those who did not drown. Why? Because many people drink soda when they go to the beach or go boating. Hardly cause and effect.

Another example of correlation would be women with higher omega-3 levels from consuming tuna and a higher incidence of birth defects. Tuna contains mercury which would of course be the cause of the birth defects. In actual fact women deficient in omega-3 fatty acids have serious health issues and so do their babies. It would be devastating to conclude that pregnant women should not consume omega-3 fatty acids from healthy sources such as contaminant-free fish oil. The same is true for men. It would be devastating if this study discouraged men or anyone else from taking a healthy source of omega-3 fatty acids.

This study uses an invalid study design, uses an invalid methodology, and makes invalid conclusions. They make statements about high levels of omega-3 fatty acids causing an increased risk of prostate cancer in subjects with low levels of omega-3. The differences in omega-3 levels between the selected controls without cancer and the subjects who developed cancer was negligible and both physiologically and clinically insignificant. This study does not offer a shred of evidence to support their conclusion that high omega-3 levels increase the risk of prostate cancer and their conclusions are at odds with a **body of evidence** supporting the benefits of omega-3 fatty acid consumption.

The FACT is that Omega-3 fatty acids found in Innate Choice Omega Sufficiency are essential nutrients and thus, by definition, required in sufficient amounts by Everybody - Everyday - For Life!