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Omega-3 and Prostate Cancer: Examining the Pertinent Evidence

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Recently, a variety of articles in the popular media have suggested that dietary consumption of long-chain omega-3 fatty acids—from fish or fish oil supplements—may increase the risk of prostate cancer. Many of these commentaries advise against the use of supplemental fish oil. In light of considerable evidence that sufficient tissue levels of long-chain omega-3s can support health in a variety of ways, these concerns need to receive careful critical scrutiny.

The Brasky Study

The basis of these reports was a new study by Brasky et al.[1] These researchers reported that in the Selenium and Vitamin E Cancer Prevention Trial (SELECT), plasma phospholipid levels of total long-chain omega-3s measured in blood samples collected at baseline correlated positively with subsequent risk of both low-grade and high-grade prostate cancer. They then reinforced this finding with a meta-analysis of previous prospective studies that have attempted to correlate blood omega-3 levels with prostate cancer risk; they found that blood levels of docosahexaenoic acid (22:6n3; DHA), but not eicosapentaenoic acid (20:5n3; EPA), correlate significantly with increased risk of total (relative risk [RR], 1.16; 95% CI, 1.03-1.31), low-grade (RR, 1.20; 95% CI, 1.04-1.38), and advanced (RR, 1.48; 95% CI, 1.10-1.99) prostate cancer, comparing the upper and lower quantiles. In their discussion, the authors raised the possibility that this association may be causal and stated that "general recommendations to increase long-chain ω-3 [polyunsaturated fatty acid] intake should consider its potential risks."[1,p.1139] Subsequently, in interviews given to the popular media, some of the authors (notably Dr Alan Krystal in his interview with NPR) advised against fish oil supplementation, although they acknowledge that few of the participants in the SELECT used such supplements, and suggested that in any case such supplementation has no demonstrable utility.

The findings from the studies that Brasky et al incorporated into their meta-analysis show considerable heterogeneity, as the authors acknowledge. In their retrospective, nested case-control study, plasma phospholipid levels of EPA, DHA, and docosapentaenoic acid (22:5n3; DPA) correlated significantly with risk of low-grade prostate cancer but not of high-grade cancer (albeit their sum correlates with high-grade cancer risk).[1] In their own previous study, Brasky et al[2] found that plasma phospholipid EPA did not correlate with risk of either low-grade or high-grade cancer, whereas DHA was linked significantly to risk of high-grade but not low-grade cancer; risk for high-grade cancer was highest in the second quartile of DHA. Crowe et al[3] found no association between plasma phospholipid DHA and prostate cancer of any grade or stage; they did report a significant positive association between EPA and high-grade prostate cancer but not low-grade, localized, or advanced prostate cancer. Park et al[4] failed to associate erythrocyte membrane levels of EPA, DPA, or DHA with total prostate cancer; they showed a nonsignificant trend toward increased risk of advanced prostate cancer with EPA but no trends in this regard with DPA, DHA, or total long-chain omega-3s. Mannisto et al[5] saw no association between EPA or DHA in serum cholesterol esters and prostate cancer risk. The only association found by Harvei et al[6] was a nonsignificant trend (P=.10) toward reduced risk with increased levels of plasma phospholipid DPA. And, in the only study that measured whole blood fatty acid levels, EPA, DPA, and DHA each showed a marked and significant inverse correlation with prostate cancer risk.[7]

Moreover, a meta-analysis addressing this same issue, published earlier this year, before data from the SELECT were available, did not observe any significant associations between

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omega-3s measured in various blood fractions and prostate cancer risk, except for a significant inverse correlation with DPA.[8] (A significant correlation of plasma omega-3s with risk of advanced prostate cancer only emerged if they excluded data from the Physicians' Health Study,[7] which they considered to be of "lower quality.")

Consumption of Fish and Fish Oil and Prostate Cancer Risk

If, however, this finding proves to be sustainable, the biological basis of the association between elevated long-chain omega-3 fatty acid levels and prostate cancer risk will remain unclear. Conceivably, metabolic factors that influence the absorption, partitioning, or oxidation of these fatty acids may also impact prostate cancer induction. Brasky et al raise the prospect that these fatty acids are playing a causative role in prostate cancer and imply that ingestion of these fatty acids from fish or fish oil supplements may increase prostate cancer risk. Yet, they fail to cite any of the pertinent evidence that bears on this point.[9] The association of fish ingestion with prostate cancer risk has been evaluated in numerous case-control and cohort epidemiologic studies. In a recent meta-analysis of these studies, Szymanski et al[10] found that case-control studies observed a modest but significant inverse correlation between fish consumption and prostate cancer risk (odds ratio [OR], 0.85; 95% CI, 0.72-1.00; P=.05); they observed no significant correlation in the cohort studies, but they found that in the 4 studies that reported prostate cancer–specific mortality, fish consumption was linked to a strong reduction in this mortality (RR, 0.37; 95% CI, 0.18-0.74; P=.005). In a case-control study that was published too late for inclusion in the meta-analysis by Szymanski et al, risk of aggressive prostate cancer was 63% lower (OR, 0.37; 95% CI, 0.25-0.54; P<.0001) in the top quartile of total long-chain omega-3 consumption than in the bottom quartile; this study also identified a variant of the *PTGS2* gene (which codes for the enzyme cyclooxygenase-2) associated with a greater than 5-fold increased risk of aggressive prostate cancer in men with low omega-3 intake.[11] Another study likewise reported an interaction between a *PTGS2* variant allele and fatty fish intake with respect to prostate cancer risk.[12] In light of suggestive evidence that cyclooxygenase-2 (cox-2) activity plays a promotional role in prostate cancer induction, it is reasonable to suspect that omega-3s might influence prostate cancer risk by modulating cox-2-dependent prostanoid production.[13] A corollary of this is that the ratio of dietary omega-3 to omega-6 may influence prostate cancer risk, consistent with the findings from a recent epidemiologic study.[14]

In men who already have prostate cancer, a regular high intake of fish has been linked to a marked increase in survival. An analysis derived from the Physicians' Health Study found that prostate cancer patients who ate fish at least 5 times weekly had a 48% lower risk of death from this disease than those who ate less than one fish meal weekly.[15] In a Swedish cohort, patients with prostate cancer in the fourth quartile of total marine omega-3 consumption were 40% less likely to die of prostate cancer during follow-up than those in the first quartile.[16] In an in vitro model of hormone ablation and evolution of androgen independence—in which androgen-sensitive prostate cancer cells grown in charcoal-stripped serum grow slowly but gradually achieve a marked increase in growth rate over 10 weeks of incubation—concurrent exposure to EPA or DHA prevented this increase in growth rate, suggesting that fish oil might slow the transition to androgen independence in patients with prostate cancer.[17,18] Diets enriched in fish oil, or in the terrestrial omega-3 stearidonic acid (18:4-n3; readily converted to EPA in the body), have slowed the growth of human prostate cancers in nude mice.[19-22]

It is, therefore, clear that current data correlate frequent fish ingestion with decreased risk of prostate cancer mortality in subjects who are cancer free and in those already diagnosed as having this disease.

We found only 2 epidemiologic studies that have attempted to correlate use of fish oil capsules with prostate cancer risk. One of these, by Brasky's own group[23] but not cited in their current article, was a prospective cohort study (VITAmins and Lifestyle [VITAL]) with a 6-year follow-up; use of fish oil supplements at baseline was not associated with subsequent risk of prostate cancer (hazard ratio [HR], 0.98). A recent analysis from an Icelandic cohort (AGES-Reykjavik) found that men consuming