MAYO CLINIC

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

Mayo Clin Proc. ■ April 2014;89(4):444-450 ■ http://dx.doi.org/10.1016/j.mayocp.2013.10.029
www.mayoclinicproceedings.org ■

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

fish oil at least once per week later in life were at a 57% significantly lower risk for advanced prostate cancer compared with those who never consumed fish oil (HR, 0.43; 95% CI, 0.19-0.95).[24]

With respect to the many large and lengthy randomized trials of fish oil supplementation that have been published, none found an increase in cancer incidence or mortality in fish oil–supplemented individuals.[25-32] And a recently published analysis from the VITAL cohort found that colorectal cancer risk was 49% lower in patients who had taken fish oil supplements at least 4 days a week for at least 3 years (HR, 0.51; 95% CI, 0.26-1.00; *P* trend=.06), in accord with previous findings from the Physicians' Health Study.[33,34] Analogously, current fish oil users in the VITAL cohort were found to be at decreased risk for breast cancer (HR, 0.68; 95% CI, 0.50-0.92).[35]

Note that the absolute levels of plasma phospholipid omega-3 measured in the recent study by Brasky et al[35] are on the low side. Total EPA+DHA levels in subjects who subsequently developed advanced prostate cancer compared with those who remained healthy were 3.74% and 3.52%, respectively. In contrast, the omega-3 index (percentage of EPA+DHA in erythrocyte membranes) in Framingham study participants who did not use fish oil supplements averaged 5.2%.[36] Although these parameters are not strictly comparable, it nonetheless is clear that few of the participants in the study by Brasky et al used supplemental fish oil, and fish consumption tended to be on the modest side. The findings of Brasky et al, therefore, do not reflect an adverse impact of high omega-3 intake and have no straightforward implications for fish oil supplementation.

Low Prostate Cancer Risk in Societies With High Omega-3 Intake

Japanese men consume approximately 8 times more fish than American men and, on average, have an omega-3 index (EPA+DHA in erythrocyte membranes)[37] of 8% to 10%, which is more than twice as high as the mean plasma phospholipid EPA+DHA content of either cases (3.66%) or controls (3.52%) in the study by Brasky et al.[38] Yet, Japan has in past decades been characterized by a rate of prostate cancer mortality many-fold lower than that of Western nations; Wynder et al[39] reported that in 1955, age-adjusted mortality from prostate cancer was less than one-seventh as high in Japan as in the United States. Consumption of marine omega-3 is even higher among the Inuit following their traditional diet; an autopsy study in the 1990s concluded that prostate cancer was extremely rare in these people.[40,41] In the authors' view, it was inappropriate of Brasky et al to raise the specter of fish and fish oil consumption as a potential inducer of prostate cancer without commenting on the wealth of existing evidence that contradicts this hypothesis, particularly in a paper that would likely be widely cited in the lay media (and indeed was, as a Google search readily confirms).

Alternative Explanations

On the presumption that the positive association of plasma long-chain omega-3s and prostate cancer risk reported by Brasky et al is confirmed in subsequent research, how might this be reconciled with the failure of dietary epidemiologic results to incriminate omega-3 in this regard? As noted, it is conceivable that some metabolic state that favors accumulation of long-chain omega-3 in plasma phospholipids also has a promotional effect on prostate cancer. For example, estrogen activity has been shown to promote the conversion of α-linolenic acid to long-chain omega-3s (accounting for the higher blood DHA levels observed in women)[42,43]; it has also been linked to an increased risk of aggressive prostate cancer, reflecting a role for estrogen receptor alpha in prostate cancer progression.[44,45] Hence, the association between long-chain omega-3s and high-grade prostate cancer in the data from Brasky et al might be driven, at least in part, by increased estrogen activity in some patients. Of related interest is the fact that hepatic delta-6-desaturase, a rate-limiting enzyme for long-chain omega-3 synthesis, is insulin inducible,[46] and insulin increases the bioactivity of plasma insulinlike growth factor 1, a key determinant of prostate cancer risk.[47]

Another possibility is that preneoplastic prostate tissue, present at baseline in patients destined to develop prostate cancer later during the study, catalyzes the conversion of α-linolenic acid to the longer-chain omega-3s owing to increased expression of delta-6-desaturase. Elevated expression of this enzyme has been reported in several types of human cancer, where

Mayo Clin Proc. ■ April 2014;89(4):444-450 ■ http://dx.doi.org/10.1016/j.mayocp.2013.10.029
www.mayoclinicproceedings.org

it may aid the activity of cox-2 and lipoxygenases by boosting the availability of their substrates.[48,49] Indeed, inhibition of delta-6-desaturase can slow the growth of certain cancers.[48] A role for cox-2 and lipoxygenase activities in the progression of prostate cancer is strongly suspected.[50,51] Any impact of preneoplastic prostate tissue on systemic levels of long-chain omega-3s would presumably be quite small, but the differential in plasma omega-3 levels between those who did or did not subsequently develop prostate cancer in the study by Brasky et al was also quite small.

Whether these specific suggestions prove to have merit, they serve to illustrate that the findings of Brasky et al do not straightforwardly indict omega-3s as a cause of prostate cancer.

Potential Cardiovascular Benefits of Omega-3

In their conclusion, Brasky et al cite a recent meta-analysis in which fish oil supplementation did not influence cardiovascular (CV) outcomes.[52] In fact, the RR for cardiac death in fish oil–supplemented patients was found to be 0.91 (95% CI, 0.85-0.98); the authors made additional statistical adjustments and set a statistical significance threshold of .0063, allowing them to claim no significant effect.

In fact, there is ample evidence that long-chain omega-3s in myocardial membranes play a physiologic role in the prevention of cardiac arrhythmias.[53] Until the past decade, controlled clinical trials almost consistently demonstrated that modest doses of supplemental fish oil could reduce the risk of sudden death arrhythmias and total CV mortality.[54] More recent controlled trials, generally enrolling patients heavily treated with modern therapies and experiencing low event rates, have failed to sustain this conclusion. Analyses by Kromhout, de Lorgeril et al, and others[55-57] have offered a credible explanation for this conundrum: Most patients enrolled in recent studies have been receiving statin therapy. Statins seem to act directly on the myocardium to reduce arrhythmic risk,[58] and this effect may render the impact of omega-3s in this regard somewhat superfluous. Indeed, a subgroup analysis of Kromhout's own "failed" Alpha Omega Trial concluded that omega-3 supplementation had, indeed, provided protection for patients not receiving statins, and the recent meta-analysis by Kwak et al notes a strong trend (RR, 0.74; 95% CI, 0.54-1.03) toward protection in the 5 included studies in which the use of lipid-lowering agents was uncommon.[56,59] (This trend almost surely would have achieved statistical significance if the large GISSI [Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico] study[27] had not been excluded for lack of a placebo control.[60]) Relatively high baseline intakes of omega-3 among the controls in recent trials—now that it is widely known that fish may be protective for CV health—may also lessen the power of these studies to demonstrate benefit with supplemental fish oil.[57] And epidemiologic studies continue to sustain the view that regular fish ingestion is associated with a lower risk of CV mortality,[61] likely owing to the fact that relatively few of the putatively healthy individuals enrolled in these studies have been using statins.

Thus, although the impact of omega-3 status on arrhythmic risk is clearly complex and conditioned by specific clinical circumstances,[62] the balance of evidence suggests that an increase in omega-3 intake by the general population would in all probability decrease the incidence of sudden death.

Because sudden death is the initial sign of coronary disease in a substantial fraction of cases, discouraging the use of fish or fish oil by the general population, absent compelling evidence that they are otherwise harmful, is highly inadvisable. And the possibility that fish oil at higher dose levels might benefit vascular health in additional ways, via various anti-inflammatory mechanisms, most notably in the context of heart failure, warrants further exploration.[63,64] The very low risk of coronary disease among traditional societies that made heavy use of marine foods, such as Eskimos and Japanese in the mid-20th century, may point to a profound protection afforded by high intake of omega-3 throughout life, albeit low consumption of red meat and trans-fats doubtless also contributes to this protection.[65,66]

Omega-3 and Brain/Eye Health

It should also be noted that DHA plays a key structural role in the brain and retina and that considerable epidemiologic research suggests that replete omega-3 status is linked to slower rates of cognitive decline in elderly individuals.[67] Although controlled trials of fish

oil supplementation in elderly populations have so far provided little encouragement on this point,[68] it is conceivable that omega-3 status earlier in life is a key determinant of cognitive function during aging. Frequent fish consumption has been linked epidemiologically to reduced risk of age-related macular degeneration, although supplemental omega-3 may not influence progression to advanced disease in patients already afflicted with this disorder.[69,70]

Omega-3 and Total Mortality

A recent prospective cohort study monitoring 2692 US adults without known CV disease at baseline examined the association of plasma phospholipid omega-3 levels measured in 1992 with subsequent total mortality over 16 years of follow-up.[71] Mortality rates of those in the top quintiles of EPA, DHA, and DPA levels compared with those in the bottom quintiles were found to be significantly lower. Comparing the top quintile of total omega-3 levels with the bottom quintile yielded an HR of 0.73 (95% CI, 0.66-0.90; $P<.001$ for trend). Life expectancy after age 65 years was 2.22 years greater in the top compared with the bottom quintile of total omega-3 concentration. These differences in mortality rates were primarily attributable to increased CV death in patients with low omega-3 levels.

Another recent study, this one a retrospective study in which patients who initiated omega-3 supplementation (1 g daily) within the 3 months after a myocardial infarction were matched with comparable patients who did not, found that subsequent all-cause mortality was 22% lower in the supplemented group (adjusted HR, 0.782; 95% CI, 0.641-0.995).[72]

Conclusion

The interesting findings reported by Brasky et al associating plasma omega-3 levels with prostate cancer risk merit follow-up in additional studies; whether their conclusions will be confirmed in future studies and meta-analyses remains to be seen, as previous pertinent studies are less than robust in affirming this correlation. In any case, their data establish association, not causation. By suggesting that omega-3s play a causative role in prostate cancer induction while failing to cite any of the ample epidemiologic evidence that contradicts this view—and, indeed, clearly points to fish consumption as a protective with respect to prostate cancer mortality—they have encouraged the media to raise fears about fish or fish oil ingestion that may have an adverse effect on overall public health. There can be little doubt that myocardial omega-3 plays a physiologic role in the prevention of life-threatening ventricular arrhythmias and that high-level omega-3 intake has the potential to benefit vascular health via additional mechanisms. The possibility that replete omega-3 status throughout life may favorably influence cognitive function and eye health as people age is more speculative but is consistent with much epidemiologic research and is credible in light of DHA's structural role in the central nervous system. And while the impact of omega-3 on risk of prostate cancer incidence seems equivocal, recent epidemiologic findings suggest that omega-3 may afford protection from breast and colorectal cancer. Recent prospective data correlating increased omega-3 levels with reduced total mortality is also reassuring. Clearly, the balance of evidence still supports the view that regular consumption of omega-3–rich foods or supplements is a prudent health practice.

Potential Competing Interests: Mr McCarty is the owner and science director of a small nutraceutical company that was one of the first to offer enriched fish oil supplements to the public some years ago. Dr Lavie has served as a speaker and consultant for GlaxoSmith Kline(GSK) and Amarin, who both sell prescription omega-3 products. Dr O'Keefe has also served as a speaker and consultant for GSK, and he is the Chief Medical Officer and founder of Cardio Tabs, a nutraceutical company that sells products containing omega-3. Dr DiNicolantonio works for Wegmans which sells products containing omega-3, but he does not profit financially from these sales.

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