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**SPECIAL ISSUE**

**DIET AND PROSTATE CANCER: Where do we stand?**

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Your comments and requests for information on a specific topic are welcome at [ecweber@nwlinc.com](mailto:ecweber@nwlinc.com)

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When the relationship of diet to prostate cancer is the issue, the appropriate question is, "What do we know for sure?" It's becoming apparent that solid, evidence-based answers are hard to come by, especially in light of the long history - 20 to 30 years - for the incubation of this cancer before it becomes clinically detectable. The research literature is loaded with *in vitro* assays that are suggestive of benefit from a wide variety of substances and by a wide variety of mechanisms, but these studies are unhelpfully rarified compared to the actual life scenario where combinations of dietary nutrients mix in the stomach, all interacting and modifying the absorption and biologic effect of each other.

Verified, clinically useful data from the usually relatively short-term dietary and epidemiological studies in humans are limited by their duration and many unavoidable methodological problems. When viewed in this perspective, "prevention" for the most part is to be regarded as an effort to retard the progression of subclinical disease at the earliest possible period in its development. Essentially, preventive measures represent an attempt to coax errant cells into a state of senescence or, better yet, apoptosis.

More easily evaluated are measures to attempt to slow progression of clinically *overt* cancer. A general consensus maintains that a "heart healthy" diet and lifestyle is a good model for attempting to control prostate cancer at any stage, but understandably, men have a strong desire for effective regimens that

*specifically* address prostate cancer. So what do we know for sure at this time as to whether dietary choices can suppress the incidence or slow the progression of prostate cancer? What nutritional candidates are best supported by evidence in *human* studies?

In general, the strongest evidence supports benefit from the consumption of oily fish, high in omega-3 fatty acids - salmon in particular; and cooked, tomato-based products, which are the optimal source of lycopene - the most efficient antioxidant, the most abundant carotenoid in plasma, and a molecule highly concentrated in the prostate gland. The higher efficiency of cooked tomato products to deliver lycopene stems from the action of heat breaking down the tomato matrix that holds most of the lycopene, a lipophilic molecule better absorbed in association with oil.

**LYCOPENE/TOMATO-BASED FOODS:** The article, “Role of Diet in Prostate Cancer Development and Progression” (JCO, Nov 2005), reported that in four studies tomato sauce reduced the incidence of prostate cancer by 25% to 80% and that in a meta-analysis of 11 case control and 10 cohort studies a high intake of tomatoes versus low was associated with an approximately 10% - 20% statistically significant reduction in prostate cancer risk. A stronger effect was seen for cooked versus raw tomatoes. In another study “tomato sauce was associated with a 35% decrease in *advanced* prostate cancer”. The venerable Health Professionals Follow-Up Study (HPFS) of 51,529 men compared a high intake of lycopene (*from all sources*) versus low, i.e., 2+ servings/week v. < 1 serving /month, and found a 16% reduction in the risk of prostate cancer. As in other studies, a stronger risk reduction, e.g. 33%, was found for high versus low intake of *tomato sauce*”, the food source with the best lycopene bioavailability.

A *slowing in the progression* of *diagnosed* prostate cancer has been recently reported from the HPFS. Men with localized and regionally advanced prostate cancer with the highest intake of lycopene (top quartile versus lowest) experienced a 44% reduction in time to PSA progression (“Diet after diagnosis and risk of prostate cancer progression, recurrence, and death (United States), by Chan JM in Cancer Causes and Control, Jan 2006”). The analysis was based on follow-up of 1202 men, appropriately stratified into clinical prognostic groups, who were diagnosed with prostate cancer during the 10 year study, 392 of whom had principally PSA reoccurrences.

There is no standardized “dose” of lycopene, but 30 mg/day is frequently recommended, and markedly elevates the plasma level. Good sources: one half cup of tomato paste, 40 mg, 8 oz canned tomato juice, 25 mg; tomato soup, 8-11 mg; and a 3” tomato, 1-4 mg.

Not surprisingly, considering the complexities of studies of this sort, not all studies support a benefit for lycopene/tomato-based foods. A January 2006 analysis of the NCI “Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial” found no evidence that lycopene intake reduced the risk of prostate cancer in the 1338 men who developed the disease, although a subset of men with a positive family history experienced a decrease in incidence (P=.04).

It would seem, however that the preponderance of available evidence currently supports the likelihood that a high consumption of tomato products - especially when cooked and processed - may reduce the incidence and slow the clinical progression of prostate cancer.

**FISH/OMEGA-3 LONG CHAIN FATTY ACIDS:** A long history of study supports the likelihood that a high consumption of oily fish reduces the incidence of prostate cancer, and, based on more recent analysis, retards the progression of established disease. The favored explanation is that long-chain fatty acids effect a reduction of the synthesis of prostaglandins, thought to promote cancer growth through promoting increased cellular proliferation.

A unique long-term study begun in 1961 (Lancet, June 2001) “studied the association between fish consumption and prostate cancer in a population-based prospective cohort of 6272 Swedish men. During the 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.”

Epidemiologists from Harvard and the NCI reported the 14 year follow-up of a cohort of 47,866 men, 2965 of whom developed prostate cancer, and found that “Eating fish more than three times per week was associated with an 11% overall risk reduction of prostate cancer, and the strongest association was for metastatic cancer [risk reduction, 26%], compared with infrequent consumption, i.e., less than twice per month” (Am J Clin Nutr, 2004 Jul). Curiously, as was found also by others, a high intake of omega-3 alpha-linolenic acid (ALA - as found in flaxseed oil) *increased* the risk of advanced prostate cancer. Delay in PSA progression in 392 prostate cancer patients following diagnosis and treatment was another finding in the Chan analysis (reference above) of the large Health Professionals Follow-Up Study: “Men in the highest versus lowest quartile of post-diagnostic fish consumption had a multivariate hazard ratio of progression of 0.73 [i.e., a risk reduction of 27%]”.

Lesser benefit and infrequently no benefit, have been found in other studies, but, once again, the preponderance of evidence suggests that increased fish consumption reduces prostate cancer incidence and post-diagnostic disease progression.

**SELENIUM:** It’s going to be long wait until 2012 when the results become available from the large SELECT trial evaluating possible benefit for selenium (Se) and Vitamin E in prostate cancer prevention. However for impatient persons, currently it could be considered a “good bet” that the intake of 200 mcg. of selenium confers benefit in lowering the risk and aggressiveness of prostate cancer. *In vitro* evidence suggests that selenium is anticarcinogenic by promoting apoptosis, inhibiting angiogenesis and cellular proliferation, and serving as an antioxidant.

However, the strength of evidence is diminished by some important qualifications. The Nutritional Prevention of Cancer Trial (NPCT) compared supplemental 200 mcg Se to placebo, and at 7.4 years of follow-up prostate cancer incidence was reduced by 64%, *but only* in those men with low baseline Se levels, i.e. <125 ng/mL.

Similar findings were reported from the analysis of the Physicians’ Health Study (PHS), best summarized in the Am. J. of Urol. Rev., Jan 2005. This study was based on 13 year follow-up data of 22,071 healthy male physicians and it evaluated the incidence of prostate cancer in relation to dietary history. A 48% reduction of the risk of *advanced*, i.e., Stage C and D, cancer was seen, *but only* was seen in the men in the lowest quintile of baseline Se levels who also had baseline PSA values of > 4 ng/mL. A comparatively high level of selenium was associated with a statistically non-significant 22% reduction in the overall incidence of prostate cancer.

The superior risk reduction seen in the NPCT trial could have resulted from the higher (190 ng/mL) mean level of Se in the NPCT patients achieved by the 200 mcg supplements compared to the mean level of 104 ng/ml seen in the PHS wherein physicians freely chose their diets.

A literature meta-analysis by Canadian researchers (Cancer Causes Control, 2005 Nov) was more generally supportive of benefit for lycopene and found a 26% risk reduction from moderate dietary Se intake (no Se supplementation). They reported that “A dose-response trend was observed when we stratified the studies by disease severity”.

Short of actually measuring the serum or toenail level of Se, an individual would be betting on the side of strongest evidence by taking 200 mcg. Of supplemental Se.

**OBESITY:** There are so many good reasons for not being overweight ... and reducing prostate cancer aggressiveness and disease progression is one of them. Multiple studies of large data bases confirm that as obesity increases so does Gleason grade at diagnosis; and that PSA failure after treatment occurs sooner; and that obesity is associated with a higher prostate cancer mortality. In short, obesity is an independent predictor of adverse outcome after treatment. It has not been established that prostate cancer incidence is higher in obese men. Instead, the implication is that obesity is associated with greater disease aggressiveness and faster progression, and not cancer initiation.

It has not been shown that weight loss *after* diagnosis improves survival, but by implication maintaining an optimal weight in the years that might precede a diagnosis a man improves his chances for having a less aggressive cancer. A report from M.D. Anderson (Clin Cancer Res, 2005 Oct) found that “men who gained weight at the greatest rate (>1.5kg/yr) between 25 years and diagnosis progressed significantly sooner (mean time 17 months) than those who exhibited a slower weight gain (mean time to progression, 39 months, P=0.005)”. A good primer on this topic is “Impact of Obesity on Prostate Cancer Recurrence After Radical Prostatectomy: Data from CaPCURE”, Bassett et al. UROLOGY 66, 2005.

The basic biologic cause of this relationship of obesity and worse outcome is not understood. Possible etiologies are obesity-induced alterations of sex hormones; increased insulin-like growth factor 1 and leptin, which both increase cellular proliferation; or obesity’s association with lower testosterone levels, which seemingly paradoxically are related to a worse pathologic stage.

This issue is becoming increasingly important as the US population fattens - 31% of American adults older than 20 years are obese. The conventional measure of “fatness” is the Body Mass Index (BMI) and a mass greater than 35 kg/m<sup>2</sup> is considered “very obese” and less than 25 kg/m<sup>2</sup>, “normal”. The Bassett article found that at a BMI of 30 - 35 kg/m<sup>2</sup> the risk of recurrence was 1.31 times that of lesser mass, and a BMI of > 35 kg/m<sup>2</sup> increased risk by 1.69 times. A chart for calculating BMI is found at <http://consumer.gov/weightloss/bmi.htm>. An example: a 5’11” man weighting 250 pounds has a BMI of 35 kg/m<sup>2</sup>, whereas at 179 pounds the BMI is 25 kg/m<sup>2</sup>.

Maintaining an optimal weight lessens the likelihood of prostate cancer aggressiveness at diagnosis, and if the cancer recurs, obesity at diagnosis portends a more rapid disease progression.

**VITAMIN E (alpha-tocopherol), GREEN TEA, and SOY PROTEIN:** In the parlance of the stock market, these would presently be best considered “weak buys” on the basis of mixed, limited, insufficient or conflicting evidence that their consumption is beneficial.

Initial encouraging findings in the vitamin E/beta-carotene cancer prevention study at first suggested a 30%-40% decrease of prostate cancer incidence, but this benefit reverted to null over time. Currently there is insufficient support to recommend 400 IU supplemental vitamin E, although there is a suggestion that this vitamin may act synergistically with lycopene and selenium.

Considerable *in vitro* studies demonstrate that the ingredient polyphenols found in green tea are inhibitory against prostate cells, but human studies are too limited. One intriguing recent study in Cancer Research, Jan 2006, showed that in a small comparative trial green tea significantly reduced the progression of HG-PIN to overt cancer.

For soy protein - the principal ingredient of which is the phytoestrogen genistein - evidence in human studies is limited, although the low incidence of clinical prostate cancer in Asia, where soy intake is high, keeps research interest in this nutrient.

**CONTRAINDICATED:** Calcium intake over 2000 mg/day, zinc supplementation > 100 mg/day, and alpha-linolenic (ALA) supplementation.

**MY PERSONAL FAVORITE:** Evidence for a 6% reduction of prostate cancer incidence from each glass of red wine per day (Int J Cancer 113:2005) - as if encouragement were needed.

And, by the way, don’t forget to eat your veggies, especially the “cruciferous” ones - broccoli, cauliflower, cabbage, and the sulforaphane containing Brussels sprouts - and exercise daily.

Have a good day!