Prostate Cancer: Epidemiology and Prevention

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Cancer of the prostate gland is the most common malignancy in men in Europe, North America, and Australia, and its relative incidence is increasing elsewhere. Little is definitively known regarding the etiology of this disease, however. Prostate cancer incidence rates do increase exponentially with age, and the neoplasm is not commonly diagnosed before the age of 50, with the average age at diagnosis being approximately 70 years. A positive, first-degree family history of prostate cancer (i.e., in a brother or father) confers increased risk and supports the existence of a heritable component to the disease. Circulating and in situ concentrations of androgens (e.g., testosterone) and growth factors are known to regulate the growth and proliferation of prostatic epithelium, and are believed to influence the development of both prostatic intraepithelial neoplasia and adenocarcinoma.

Considerable international variation in the incidence of and mortality from clinical prostate cancer, along with observations of changing risk in populations that migrate from low to high rate areas (or vice versa), suggest that environmental factors play an important role in its development. For example, Black men in the United States have higher incidence and mortality rates compared to White men in the same country, and far higher rates than do Black men in Africa. Dietary factors have been extensively studied in this regard, although a consensus has yet to be reached regarding any of the potentially protective or harmful nutritional components. As described in detail here, in recent randomized and controlled trials two micronutrients, vitamin E and selenium, have demonstrated the potential for primary prevention of prostate cancer, and have generated considerable interest in the development of confirmatory studies. Other characteristics that have been investigated and that may be related to risk include cigarette smoking,
vasectomy, increased sexual activity, infectious agents (e.g., human papilloma virus), and occupational cadmium exposure [1].

Prostate cancer presents in two forms: (1) latent, microscopic foci of low-grade adenocarcinoma that are primarily discovered incidentally during transurethral resections for benign prostatic hyperplasia and enlargement, or in autopsies, and (2) clinical, symptomatic prostate cancer that entails morbidity and mortality. Substantially lower cross-population variation in rates of subclinical disease as compared with the latter supports a role for modifiable exposures, including diet, in the progression to (or the selection of) more invasive disease. Related is the fact that extensive use of prostate-specific antigen blood testing beginning in the late 1980s led to a dramatic rise in the detection of early prostate cancer in the United States, for example, with little or no change in mortality rates.

**Laboratory Experiments**

A direct influence of diet on prostate carcinogenesis has been demonstrated in mice and rats. Early experiments supported a tumor growth promotional role for higher fat diets [2], while recent work points to a more powerful effect of total energy consumption and not lipid intake *per se* [3, 4]. Other nutritional factors for which at least some experimental data exist to support a possible inhibitory effect on prostate tumorigenesis include retinoids, vitamins D and E, flavonoids, and selenium [4]. Prostate cancer cell culture experiments have shown tumor cell growth inhibition in response to tocopherols, carotenoids, and retinoids [5], and in one experiment, stimulation of growth by linoleic acid [6]. Many of these experimental findings support the nutrient-prostate cancer associations observed in human populations and described below.

**Epidemiological Studies and Clinical Trials**

Human case-control and cohort studies, along with randomized trials, have provided substantial evidence concerning the role of dietary factors in human prostate cancer. Dietary fat and carotenoid intake along with meat consumption have received the greatest attention to date, yet some promising leads have emerged recently from investigations of other nutrients, including vitamin E and the trace element selenium. For organ sites such as prostate cancer that show highly variable rates of occurrence internationally, hypothesis-generating correlative studies can provide clues regarding possible etiologic factors, including dietary components. One recent analysis of prostate cancer mortality among 59 diverse populations showed significant inverse correlations between the rates of disease and estimated *per capita* intake of dietary energy from cereals and oil seed sources, nuts, and fish, and positive correlations for total energy and fat, and
energy from animal food sources [7]. These factors collectively accounted for approximately 90% of the observed international variation in prostate cancer mortality.

Dietary Fat, Meat, and Dairy Products

The role of fat (or lipid) consumption in prostate cancer has been intensively studied for nearly two decades. Early ecologic analyses revealed positive correlations between *per capita* dietary fat “consumption” (actually, population-based food disappearance) and incidence and mortality rates [8], as did the most recent such study [7]. Subsequent case-control investigations fairly consistently show elevated risk – typically by 50–200% – for higher intake of both total and saturated or animal fat [9–12]. In one of these investigations [12], a stronger link was made for animal fat intake among the higher-risk population of Black Americans and for more advanced prostate cancers in both Black and White men. Some of the studies show positive relationships with dietary energy, or with meat or dairy product consumption, factors having a high collinearity with dietary fat. Of the cohort studies, only a few show a positive relationship between fat intake *per se* or intake of fat from animal sources and prostate cancer risk [13]. Several other investigations support instead an etiologic role for red meat consumption specifically [14]. A specific risk increase for either high dietary intake [13] or elevated plasma concentration [15] of α-linolenic acid, the polyunsaturated essential fatty acid of the ω–3 series found in both meat and vegetable oils, has also been demonstrated. Other human data for dietary polyunsaturated fat intake are limited and inconsistent, showing positive, null, and inverse risk relationships.

Carotenoids, Vegetables, and Fruit

The prostate cancer preventive potential of dietary carotenoids – or carotenoid-rich vegetables and fruit – has been intensively studied. Even so, the true relationships for these dietary constituents remain, to date, obscure, with beneficial and harmful associations having been shown in several studies. For example, cohort and case-control studies have shown higher risk [16], lower risk [10, 17], and no risk [18] for prostate cancer among men with increased dietary β-carotene intake, or increased risk for higher as compared with lower serum concentrations [19]. The findings for vegetable and fruit consumption are also equivocal, suggesting either little, if any, etiologic role, or substantial inter-population differences in the specific foods consumed [20]. Most recently, studies have begun to show a protective relationship for lycopene and tomato food products in some populations [21].

Supplementation studies provide additional valuable information regarding the possible effects of micronutrients on the development of cancer in controlled settings. No material effect of chronic β-carotene supplementation on prostate cancer incidence was seen in three large double-blind, randomized prevention trials, the Alpha-Tocopherol, Beta-Carotene (ATBC) Study [22], the Physicians’
Health Study [23], and the Beta-Carotene and Retinol Efficacy Trial (CARET) [24]. These studies tested daily dosages of 20, 25, and 25 mg, respectively, and in the latter trial, β-carotene was combined with retinyl palmitate (25,000 IU). The relative rates of prostate cancer in the β-carotene groups compared to those not receiving β-carotene were not significantly different from 1:1.23 in the ATBC Study, 0.99 in the Physicians’ Health Study, and 1.01 in the CARET.

Vitamin E (Tocopherols and Tocotrienols)

A potentially far-reaching lead relevant to the prevention of prostate cancer came from the large controlled chemoprevention trial conducted in Finland [22]. The ATBC Study was a double-blind, placebo-controlled intervention trial testing whether α-tocopherol or β-carotene supplementation prevents the occurrence of lung cancer and other cancers. The trial was conducted between 1985 and 1993 in southwestern Finland as a joint project between the National Public Health Institute of Finland and the US National Cancer Institute. It was based on epidemiological studies showing lower risk of cancer among persons consuming more fruits and vegetables and persons with higher serum levels of antioxidant vitamins such as β-carotene and vitamin E, and on the known biological properties of these substances. The trial enrolled 29,133 male cigarette smokers who were 50–69 years old and randomized to one of four study groups based on the $2^2$ factorial design: β-carotene alone (20 mg/day, as 10% water-soluble beadlets); vitamin E alone (50 mg/day, as dl-α-tocopheryl acetate); both agents, or placebo. Active intervention continued for 5–8 years (median follow-up was 6.1 years). Incident cancers were identified through the Finnish Cancer Registry.

By the end of the ATBC Study, a statistically significant 32% decrease in the incidence of prostate cancer was observed in the α-tocopherol arm compared to those not receiving α-tocopherol, based on 246 cases. The reduction was evident in clinical prostate cancer, with α-tocopherol lowering by 40% the incidence of more advanced cancers (i.e., tumors of stage B–D). Prostate cancer mortality was also 41% lower in the α-tocopherol arm. These intervention effects were observed at all levels of dietary vitamin E and fat intake, and in younger and older men. Also, they were not due to changes in serum prostate-specific antigen or in diagnoses of benign prostatic hyperplasia, both of which were similar across the supplementation groups. We interpreted the stronger effect of vitamin E on clinically evident and invasive cancers as evidence of a tumor growth inhibitory effect as opposed to diminished malignant transformation of normal prostatic epithelium.

This very promising clinical trial-based effect has enormous public health implications in that it represents a simple, practical intervention with the potential to inhibit the development of this most common cancer in men throughout the world. Both a confirmatory trial of vitamin E and investigations of the several potential mechanisms through which this micronutrient may have impacted prostate cancer are underway.
Epidemiologic studies have also provided data supportive of a protective association for vitamin E in prostate cancer. Several prospective studies of serum or plasma vitamin E (usually \( \alpha \)-tocopherol) show lower concentrations in cases, years prior to diagnosis, as compared to men who later did not develop the disease, with the relative risk decreasing at higher levels [25, 26]. Higher pre-study, total vitamin E intake (i.e., diet plus non-study supplements) was also related to decreased prostate cancer risk in the \( \alpha \)-tocopherol supplementation arm of the ATBC Study [27]. The observational data therefore complement the aforementioned trial result and when taken together provide strong evidence to support a beneficial influence of vitamin E in prostate carcinogenesis.

Selenium
A possible role for selenium intake and biochemical status and prostate cancer is supported by a few cohort studies and, importantly, results from a recent intervention trial. The strongest cohort-based findings in terms of the number of cases evaluated \( (n = 181) \), quality of selenium assessment, and magnitude of relative risk estimates come from a nested case-control study of toenail selenium concentration, a solid measure of long-term selenium intake [28]. This recent investigation showed a 65% lower risk of advanced prostate cancer for men in the highest category of selenium status. Case selenium concentrations were 15% lower than those of controls. Other prospective studies have shown no association for serum selenium [29] or dietary selenium intake [27], although estimation of true dietary selenium intake is difficult due to the substantial geographic variation in soil selenium content that results in variable food composition.

A strong preventive effect was observed for selenium supplementation in the Nutritional Prevention of Cancer Trial [30]. In this randomized, double-blind study conducted in the US, a significant 63% reduction in prostate cancer incidence was observed \( (13 \text{ versus } 35 \text{ cases}) \) after 4.5 years among men in the selenium yeast group \( (200 \mu g \text{ elemental selenium daily}) \) as compared with the placebo group, providing trial-based evidence for a possible beneficial role of selenium in this disease.

Vitamin D and Calcium
It has been hypothesized that prostate carcinogenesis may also be related to vitamin D status, based in part on geographic variation in both exposure to sunlight and in incidence rates [31]. Case-control investigations of prediagnostic serum have not generally supported an etiologic relationship, however. One study observed low serum concentrations of \( 1,25 \)-dihydroxyvitamin D in cases as compared to controls [32], while three more recent reports have shown no association for either this metabolite, or its precursor, \( 25 \text{-hydroxyvitamin D} \) [33–35].

An essential mineral related to vitamin D metabolism, calcium, has also been preliminarily linked to prostate cancer, with higher calcium intake predicting an increased risk of clinical disease in some studies [36, 37]. Data from other investi-
gations fail to support the hypothesis, however [12, 38]. Based on our current knowledge, the role of these micronutrients therefore remains rather speculative.

**Other Factors**

There is little definitive evidence to support a relationship between alcohol (ethanol) consumption and the development of prostate cancer. Only two prospective studies suggest an elevated risk for beer drinking [18] or for daily alcohol consumption among non-smokers only [39], while two others [40, 41] and case-control studies [42] show no association.

Two other diet-related (i.e., particularly vis-a-vis energy), anthropometric characteristics potentially related to androgen metabolism or growth factors and therefore prostate carcinogenesis are adiposity, as usually estimated by body mass index (kg/m²), and adult height. As reviewed earlier, body mass index and height are relatively weak predictors of risk [43]. As exemplified by two recent studies, 20–40% excess risk has been observed for taller compared to shorter men in longitudinal cohorts [44, 45], and for high body mass index, or obesity [45].

**Conclusions**

Although during the past decade a substantial volume of research has investigated the etiology of prostate cancer, we have only a few convincing leads regarding how to prevent the disease through dietary and nutritional means. Recent findings from two randomized, controlled cancer intervention trials provided strong evidence that supplementation with either vitamin E or the trace element selenium may have a real and important preventive role in this important malignancy. Studies aimed at confirming these results are imperative. The potential benefit from a reduction in animal fat intake, and possibly meat consumption, is supported by a large body of research, although most studies have not eliminated total calories as the effective exposure. Whether other nutritional factors such as carotenoids, vitamin D, alcohol, and overweight have true etiologic relationships with prostate cancer can only be answered through further investigation.

**References**


**Discussion**

*Dr. Badruddin:* Can I start off by asking by how much the discovery of the different dietary factors that contribute to prostate cancer has led to a reduction in the incidence worldwide?

*Dr. Albanes:* The effect is potentially quite large. We couldn’t begin to add the relative risk reductions that are suggested from many of the studies because we would end up with less prostate cancer than even theoretically possible. There must be overlap. As discussed earlier, the individuals who report consuming much more animal meat and saturated fat are, on average, more likely to consume fewer fruits and vegetables. That same kind of dietary pattern is related to obesity, and perhaps also to earlier childhood exposures that promote growth, and to a number of other factors. I don’t have a precise answer to your question but I believe that if we can corroborate several of the associations shown here, leaving aside the inherent genetic background predisposition, we could potentially prevent up to 50% of clinically relevant prostate cancers.
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*Dr. Steenhout:* In your prospective study, you plan to use selenomethionine. Why did you select that? What is the advantage over using selenite?

*Dr. Albanes:* To begin with, the data from Clark et al. [30] show that selenomethionine was the major moiety of selenium in selenized yeast. Approximately 50% of the elemental selenium is in the form of selenomethionine. That is one important consideration. The other is the lesser toxicity of organic preparations such as \( L \)-selenomethionine and \( L \)-selenocysteine, for example, compared with selenite or selenate.

*Dr. Gianotti:* How did you come up with the dose of vitamin E and selenium in the selenium-supplementation trial? Are they based on a dose-response study?

*Dr. Albanes:* No, there has been no real dose-response study. Our choice was in large part empirical. For vitamin E, for example, we have the observation from the ATBC trial that 50 mg is beneficial. However, there was a very strong view from participating oncologists that we should try to maximize the potential benefit, given the safety record for vitamin E in other large population trials that have used 600 or 800 mg with complete safety over many years. Thus in the end 400 mg was decided upon. Another reason for this was a desire to prevent secondary endpoints, such as coronary artery disease and ischemic strokes. With selenium, toxicity was more of an issue. The nutritional prevention of cancer trial of Clark et al. [30] showed benefit from 200 \( \mu \)g of elemental selenium, and there was less enthusiasm for going to higher dosage, knowing the potential toxicity.

*Dr. Biswal:* In the ATBC trial, you mentioned that vitamin E has reduced the incidence of prostate cancer by 20%. In that trial, did they include patients already under treatment for prostate cancer?

*Dr. Albanes:* The participants in the trial were all cancer-free at the start of intervention. Thus the effect that I described of a one third reduction in prostate cancer incidence was in the setting of patients with no known clinical disease. However, we did not examine the prostates formally at baseline, so there might have been microscopic or even subclinical lesions that would have been diagnosed within the following years in both treatment groups.

*Dr. Endres:* In Keshan disease in China, which is believed to be caused by deficiency of selenium and perhaps some other genetic or environmental factors, it might be interesting to determine whether affected men have an increased incidence of prostate cancer. Is anything known about that?

*Dr. Albanes:* We have conducted similar nutrition prevention trials in China, involving a province where Keshan disease is prevalent. The commonest cancers were esophageal and gastric. Very few prostate cancers were reported. This could be accounted for either by not having sufficient men entering the age groups where prostate cancer incidence is important. But it’s an important reminder that we should specifically look at very low selenium areas.

*Dr. Mason:* Given the very strong and consistent associations between total energy intake, total fat intake, animal fat intake, and prostate cancer incidence, why is body mass index (BMI) not seen as a consistent association? You would think that it would be, and yet I think you stated in your discussion that in most of the studies that have looked at BMI, such an association is not seen. Why is that?

*Dr. Albanes:* I’ve been puzzled by that as well. It may be qualitative, such that the relevant risk factor is not total fat but a component of the fat or of the meat itself. Perhaps certain fats or fatty acids affect androgens very specifically and that is not reflected in the BMI.

*Dr. Argiles:* Obesity is a complex pathology and it doesn’t only depend on food intake. BMI is also dependent on energy expenditure. We have to assume that some people are just obese because they eat a lot and others are obese because they have other problems. Maybe this accounts for the discrepancy between BMI measurement and the incidence of prostate cancer.
Dr. Albanes: A point well taken, and especially in that there are some data that point to a beneficial effect of physical activity in prostate cancer.

Dr. Hursting: It has been shown that heterocyclic amine formation resulting from high-temperature cooking of meats and other foods targets the prostate in animal models [1]. Are there any data adjusting animal fat intake by cooking methods?

Dr. Albanes: New dietary instruments are being developed to include the method of cooking, particularly the charbroiling or the browning of meats during the preparation of the food. I believe this refinement of the data will enhance our knowledge of the risk factors.

Dr. Goldbohm: I’m not familiar with all the studies on prostate cancer, but for colorectal cancer there have been 14 prospective cohort studies on meat consumption and colon cancer risk. Only five of these found strong effects related to meat consumption, and none of the other studies found any effect. The studies that found an effect were all American. Studies from elsewhere, a Swedish study for example, found no effect. I’m not confident that the animal fat or the meat hypothesis is a satisfactory explanation for prostate cancer. If similar factors are involved in colon cancer and in prostate cancer, then there may be some other environmental factor that explains why meat products appear to be an important risk factor in some populations but not in others. I think we have to do more studies looking carefully at preparation methods to get a more definitive answer, which we haven’t achieved in the colorectal area.

Dr. Pichard: I’m wondering, though this might be a crazy question, if epidemiologists sometimes think about what should be removed from our daily lives in order to decrease risk, rather than what we should take every day to decrease risk? Does that make sense?

Dr. Albanes: I like that question very much. I believe all epidemiologists have a perspective and are not necessarily fixed upon either trying to add something to our busy schedules or upon what we should take away. This brings to mind a recent talk I heard where a researcher suggested that we should take television away so that the children wouldn’t be so obese, with all the problems obesity brings in later life and even in the near term. I would say the results I presented for vitamin E and selenium suggest the value of adding something specific, such as a supplement, to our daily food intake for the prevention of cancer. We have much evidence from observational, case-control, and cohort studies that vegetable and fruit intake is a very important feature of the diet which can be recommended for a number of other reasons as part of a healthful lifestyle.

Dr. Goh: I’ve listened to your lecture with great interest. I think you’ve outlined the fact that selenium and vitamin E play an important role in preventing prostate cancer. What about the role of β-carotene? I was concerned about the data that Dr. Wang presented earlier in relation to excess β-carotene. This is a very widely prescribed supplement. Do you think it has anything to do with prostate cancer? If it has been shown to have a deleterious effect, maybe we should avoid it altogether, rather than advising lower doses and taking other supplements as well.

Dr. Albanes: The three trials that Dr. Wang referred to also presented data regarding the effects of β-carotene on prostate cancer. In none of the three trials was there a significant impact. In fact, in two of the trials a zero effect was observed, though of the three, only the Physician’s Health Study involved a large number of non-smokers. However, in light of the epidemiological findings I showed for β-carotene and for vitamin A, where some studies have suggested possible harm in prostate cancer, I believe a much more detailed investigation is needed.

Dr. Muti: I have a methodological question. How will you deal with latent prostate cancer in your follow-up? I’m expecting that some of the prostate cancers you will find would be identified by a screening program of the population or some other kind of intervention, so I think that you will have the problem with latent prostate cancer.

Dr. Albanes: That’s an important point which I neglected to emphasize. In ATBC we may in fact have had a number of the men with latent microscopic foci, and what we believe
the vitamin E/tocopherol preparation probably did – if in fact it was a real effect, which we believe and hope it is – was to have acted in a tumor-promotional phase that was described by Dr. Hursting in terms of the sequencing, such that in the vitamin E group there was an inhibition or slowing of that progression or growth from microscopic or latent disease to clinically full-blown diagnosed prostatic cancer. In fact we have initiated studies that have looked at our vitamin E versus our placebo group to examine biological variables such as testosterone, androstenedione, and IGF-1, for example, factors that are known to affect the glandular epithelium of the prostate and other organs, to see whether there was a meaningful effect of the agent on biological variables that could be thought to inhibit progression from latent to clinically relevant cancers.

Dr. Kho: In your trials, do you see a decrease in the aggressiveness of prostate cancer in patients who were supplemented with vitamin E and selenium? For example, are there fewer patients with hormone refractory prostate cancer, or do they develop earlier stages of prostate cancer without metastatic disease?

Dr. Albanes: Our results showed no material impact on stage 0 and stage 1 or very early A lesions within the trial. Because of the amount of work required to distil this kind of information, we haven’t yet investigated this any further. We did analyze survival time and other basic variables and found no effect. But I agree with you that more detailed investigation of the records for the cases in the E group versus the non-E group might shed more light on that question.

Dr. Bostick: Your rationale for the dose in this trial seems to follow that of the two previous trials – that is, if a little is good for you then a lot might be better. This seems to point out the need for studies to determine the optimal dose, and such studies could be of the biomarker type. So, for instance, in a vitamin E study, there might be biomarkers of oxidative damage. Why has this trial apparently leapt over that step, which seems a necessary one?

Dr. Albanes: I can agree with you on all of that. There are several reasons for not pursuing dosage studies. One has to do with the good safety record of these agents available already from large randomized trials such as the women’s health study, which I believe is using 600 units of vitamin E daily, and the CHAOS trial conducted in Great Britain that used a very high dosage without ill effects. Both of these very large studies and other data, for example on β-carotene use obtained in the 1980s, suggested that these agents were safe in the dosage chosen. In terms of weighting, I agree with you that those kinds of biomarker studies would be very useful. The trial won’t actually get started for at least another year and hopefully during that time some of this type of work can be obtained and shed some additional light on dose. At present the investigators, after many discussions looking at a variety of data from many studies, have settled on these doses.

Dr. Wang: I think that when we talk about the dose of β-carotene, we need to consider the specific organ. The lung is a unique organ because it’s open to the air, so when high-dose β-carotene accumulates there it may be unstable and you may need other antioxidants as well, but in the prostate or the liver or kidney, the situation is quite different from the lung. That’s just a comment.

Reference