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REVIEW ARTICLE

Diet, lifestyle and risk of prostate cancer

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Abstract
Prostate cancer has become a major public health problem worldwide. Yet, the etiology of prostate cancer remains largely unknown. Dietary factors, dietary supplements, and physical activity might be important in the prevention of the disease. In the majority of studies, it was observed that high consumption of meat and dairy products has been linked to a greater risk. In contrast, frequent consumption of fatty fish and tomato products has been associated with a reduced risk. It has been shown consistently that high levels of circulating insulin-like growth factor 1 (IGF-1) are associated with an increased risk of prostate cancer. Dietary factors are also recognized as determinants of circulating IGF-1, thus changes in diet may influence IGF-1 concentrations in serum. Furthermore, increased intake of vitamin E and selenium (from supplements) has been shown in intervention studies to decrease the risk. Possibly, high level of physical activity is also associated with decreased risk of prostate cancer. The accumulated scientific evidence concerning the associations between diet, lifestyle, and risk of prostate cancer development suggests that there are some identified modifiable risk factors that it might be recommended to change in order to decrease the risk for this common cancer site.

Despite a substantial morbidity and mortality, the etiology of prostate cancer remains largely unknown. The only established risk factors are age, race, and family history of prostate cancer. For more than 30 years, researchers have struggled to identify the etiological factors that might explain the almost 40-fold difference in the reported incidence and the about 12-fold difference in mortality of prostate cancer between various geographic and ethnic populations [1].

Although it was estimated that 40% of prostate cancer can be explained by genetic factors [2], there is strong evidence from migrant studies that lifestyle and environmental factors also have an influence on the development of this neoplasm. Among migrants moving from countries with a low prostate cancer incidence—such as Japan—to North America, the incidence increases to almost equal that of white Americans within a generation. Therefore, the large geographic differences observed in morbidity and mortality are not due to genetic variation only. Men from the same ethnic group but raised in different environments have a risk of prostate cancer comparable to the incidence in the country where they live, not their country of origin [3].

Although several genetic factors that predispose to prostate cancer have been discovered, an environmental trigger is probably necessary for manifestation of the disease. This should be true even for carriers of strong cancer-susceptibility genes because only a minority of those men will develop the disease.

Although the etiology of prostate cancer is still not well known, there are some environmental factors that have been reported to be associated with an increased risk of prostate cancer development and mortality, and others that have been associated with a decreased risk.

Among these environmental factors, diet has been suspected to play a major role in the initiation, promotion, and progression of prostate cancer. The purpose of this review is to summarize the available epidemiological evidence regarding the association between diet, lifestyle and risk of prostate cancer.

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Dietary factors possibly associated with increased risk

The most convincing epidemiological data on diet and prostate cancer are those regarding the association between a high consumption of dairy products/meat products and increased risk of prostate cancer.

Dairy foods seem to be the most consistent dietary predictors for prostate cancer in the published epidemiological literature. Overall, 7 of 9 cohort studies and 12 of 14 case-control studies observed a positive association for some measure of dairy products and prostate cancer [4].

Only two studies analyzed separately advanced and metastatic prostate cancer [5,6]. These suggest that the association might be stronger for the more advanced cancers than for all prostate cancers, which might indicate a potential role of dairy products in the progression of this neoplasm.

Mechanisms behind these observed associations are not yet known. Previously, it was speculated that the fat content of dairy products may affect the risk of prostate cancer. However, a few recent studies using comprehensive dietary assessments did not confirm the fat hypothesis [5,6]. Moreover, in the latter study, skimmed milk and low fat milk were positively associated with prostate cancer [6].

Several studies have reported that calcium may play an important role in prostate cancer development. The strongest evidence for an association between calcium and risk of prostate cancer comes from the Health Professionals Follow-up study [6], which had a comprehensive dietary assessment of calcium from food as well as from multivitamins, calcium supplements, and other sources (e.g. antacids). In that study, men who consumed more than 2000 mg of calcium per day had an almost fivefold increased risk of metastatic and fatal prostate cancer in comparison with men who consumed less than 500 mg. The mechanism behind the positive association between calcium intake and the development of prostate cancer may be linked to the regulation of levels of 1,25 dihydroxyvitamin D_3 ($1,25(OH)_2D_3$). It has been shown that high serum levels of calcium suppress the production of $1,25(OH)_2D_3$ as a result of a decreased production of parathyroid hormone [7]; $1,25(OH)_2D_3$ has been shown to inhibit prostate cancer cell-growth, development, and progression [8].

Speculation about another possible biological mechanism behind the observed positive association between high dairy food consumption and prostate cancer involves insulin-like growth factor-1 (IGF-1). There is strong evidence that an elevated concentration of circulating serum IGF-1 is associated with an increased risk of prostate cancer, as recently presented in a meta-analysis [9]. High consumption of low-fat milk has been linked to a higher concentration of circulating IGF-1 [10]. Thus, the observed positive association with dairy foods may partially be due to increased levels of IGF-1. However, this hypothesis is speculative and requires further studies regarding the determinants of circulating IGF-1 concentrations.

Among epidemiological studies, 17 of the 23 case-control and cohort studies summarized in the review by Kolonel showed a positive relation between high consumption of meat and increased risk of prostate cancer [11]. All these studies but one have shown at least a 30% increased risk related to high meat consumption. Of the eight studies that distinguished red meat as a separate group or that included specific red meat items (mostly beef or pork), all but one found positive associations, six of which showed 30% increased risk or more. Observed associations with red meat seemed to be stronger than with total meat. Furthermore, higher risk estimates have been observed for advanced and metastatic tumors than for all prostate cancer tumors: risk ratio (RR) = 2.0 (advanced) versus 1.4 (all) for red meat and 2.2 (metastatic) versus 1.5 (all) for total meat [5]. These results might suggest a role of meat in the progression of prostate cancer.

Although the biological mechanisms by which high meat consumption could be associated with an increased risk of prostate cancer development are not known, several possible explanations have been proposed. First, it has been speculated that the observed positive association with meat reflects a high intake of fat. However, the findings on total dietary fat and specific types of fat (saturated, monounsaturated, polyunsaturated) and prostate cancer risk are not consistent [11]. Second, diets that are high in meat and other animal products may be low in plant foods (fruit and vegetables, whole grain cereals, beans, etc.) [12]. In consequence such diets may be relatively deficient in certain anticarcinogenic constituents, such as antioxidants and phytoestrogens, or other phytochemicals influencing sex hormone metabolism, such as for example 5-alfa-reductase inhibitors present in beans. Third, pan frying and grilling of meat in high temperature results in the formation of heterocyclic amines, which are potent carcinogens in animal studies [13], including the rat prostate [14]. Fourth, red meat is a major source of zinc, which is essential for testosterone synthesis and may have other effects in the prostate [15]. A recently published study has shown that use of zinc supplements is associated with an increased risk of prostate cancer [16]. Men who used 100 mg or more zinc per day had a 2.3-times increased risk, and men who took

supplemental zinc for 10 years or more had a 2.4-times higher risk of advanced prostate cancer than non-users of zinc supplements. Finally, we have recently observed that high red meat consumption and high protein and zinc intake are correlated with higher concentrations of circulating IGF-1 (zinc) [17].

Smoking and risk of prostate cancer

The role of smoking in prostate cancer is not clear. Most of the prospective cohort studies and all nested case-control studies that used incident prostate cancer cases in analyses observed no association between current smoking and risk of prostate cancer development (for review see reference Hickey et al., 2001 [18]). However, in a large cohort of 135 000 Swedish construction workers where over 2 300 subjects developed prostate cancer during 20 years of follow-up, a weak (11%) but statistically significant increased risk was observed [19]. Moreover, in two American cohorts, one from California [20] and one from Iowa [21] there was a significant positive association between current smoking and risk for development of prostate cancer. In the Swedish and in the Iowa cohort there was a significant dose–response relation.

For comparison, 14 of 20 population-based case-control studies and 12 of 16 hospital-based case-control studies observed no association between current smoking and incidence of prostate cancer (for review see Hickey et al., 2001 [18]). However, owing to their retrospective design these studies may suffer from several methodological shortcomings.

In contrast to findings regarding smoking and incident prostate cancer, the majority (8 of 12) of the prospective studies that used death from prostate cancer as the outcome (instead of incidence) found a positive association between current smoking and prostate cancer.

The Health Professional Follow-Up Study found that men who had smoked 15 or more pack-years of cigarettes within the preceding 10 years were at a higher risk of metastatic prostate cancer (RR = 1.81, 95% CI 1.05–3.11) and fatal prostate cancer (RR = 2.06, 95% CI 1.08–3.90) relative to non-smokers. This study also found a significant dose–response relation between smoking over the prior 10 years and metastatic and fatal cancer [22]. However, an average risk estimate based on the prospective studies was not strong—in the order of approximately 30% increase.

To determine whether the relatively consistent observations of positive association between smoking and fatal prostate cancer reflect smoking-induced aggressiveness or a bias, more detailed studies are needed. Data need to be analyzed by stage and grade in relation to recent smoking and careful control for potential confounding factors such as history of screening and treatment received by prostate cancer cases will also be of importance.

Potentially protective dietary and lifestyle factors

It is recommended to eat at least five portions of vegetables and fruit daily to prevent cancer generally, but it is unknown whether this protects against prostate cancer specifically. The Working Group regarding fruit, vegetables, and cancer at the International Agency for Research on Cancer (IARC) concluded that the available evidence for fruit is consistent and suggests that high fruit consumption does not reduce prostate cancer risk [23]. For vegetables, the majority of studies have reported a slight but not significant lower risk for high consumption. Because vegetable consumption is measured with substantial error in epidemiological studies, the Working Group could not exclude the possibility that vegetable consumption may be associated with a small decrease in the risk of prostate cancer.

The relationship between dietary intake of tomatoes and tomato-based products and the development of prostate cancer has been reviewed previously by Giovannucci [24]. Several studies, although not all, have demonstrated a significant inverse association: high consumption of tomatoes and tomato products has been associated with 15–50% lower risk of prostate cancer in two cohorts but not in two others, and in three case-control studies but not in two others. The inverse association between tomatoes/tomato products and prostate cancer risk has been linked to lycopene, a carotenoid present in tomatoes that has been shown to have strong anti-oxidative properties and to suppress the growth of prostate cancer.

Several studies of the relationship between vitamin C and the risk of prostate cancer have yielded conflicting results. Most of the studies have found no association between increased serum or dietary vitamin C content and reduced risk of prostate cancer. Vitamin C, present in vegetables and fruits, is unlikely to affect the risk of prostate cancer.

Regarding vitamin E, another anti-oxidant found predominantly in vegetable oils, nuts and nut oils, egg yolk, and some fruits and vegetables, the evidence is intriguing. Results from the Alpha-Tocopherol Beta-Carotene Cancer Prevention Trial among smokers have shown a significant 40% reduction in prostate cancer incidence and mortality among men receiving 50 mg supplements of vitamin

E (alpha-tocopherol) daily [25]. In the Physician's Health Study, null associations with self-reported vitamin E supplement intake were observed in the whole cohort, but there was a borderline, statistically significant 50% lower risk of metastatic and fatal prostate cancer among smokers taking vitamin E supplements [26]. Furthermore, a study of serum vitamin E reported statistically significant inverse associations with fatal prostate cancer among the subgroups of smokers [27].

Frequent fish consumption, especially fatty fish, has been reported to be inversely associated with prostate cancer risk. In a population-based prospective cohort of Swedish men with 30 years of follow-up, those men who never or seldom ate fish had significant 3.3-times higher risk of fatal prostate cancer and 2.3-times higher risk of all prostate cancer than those who consumed fish frequently [28]. The biological mechanism behind this association might be linked to eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which are found in fish oils [29]. EPA competes with arachidonic acid. Therefore a high intake of EPA can lead to important changes in the relative concentrations of tumor-growth-enhancing prostaglandins. DHA has been shown to activate peroxisome proliferator activated receptor-gamma (PPAR-gamma) which may result in inhibition of the growth of prostate cancer cells and in the induction of apoptosis. This might explain the stronger association observed for fatal prostate cancer than for all prostate cancer, and suggests that fish compounds may play an especially important role in cancer progression. Moreover, fish is a good source of vitamin D and selenium, both of which are considered to have anti-carcinogenic properties.

Another nutritional factor often mentioned in the context of prevention of prostate cancer is selenium, an essential non-metal trace element present in grains, fish, eggs, meat, and dairy products. The level of selenium in the soil, which varies according to geographic region, determines the level of selenium found in the plants grown in that area. Recent results from the prospective Physicians' Health Study, showing an inverse association between plasma selenium levels and risk of advanced prostate cancer, suggest that higher selenium levels may slow prostate cancer progression [30]. One of the previous principal studies on the role of selenium in reducing the risk of developing prostate cancer has shown that supplementary intake of selenium was associated with lower risk of developing prostate cancer [31]. Results from this small intervention study were so promising that they led to the initiation of the randomized, double-blind Selenium and Vitamin E Cancer Prevention Trial (SELECT) that started in 2001 [32]. This randomized trial, sponsored by the US National Cancer Institute, has randomized over 30 000 healthy men to the treatment and placebo groups, and will follow them over a 12-year period and monitor the incidence of prostate cancer in each of these groups. In year 2014, we expect more definite results from this study showing the effectiveness of chemoprevention with selenium and vitamin E regarding prostate cancer development.

Plant foods contain quite large amounts of phytochemicals—other than the above mentioned—with a wide range of biological properties. Those with oestrogen-like activities—phytooestrogens—have received a great deal of attention in recent years. Among them there are two major groups: isoflavones, found in larger amounts in soy beans and soy products, and lignans, for which flax seed is a particularly rich source. Several studies using animal models of prostate cancer have shown the protective effect of isoflavones as well as lignans; however, recently reviewed results from epidemiological studies are not consistent [33].

Physical activity is one important modifiable lifestyle factor that has been studied in relation to prostate cancer. Despite several methodological differences between studies, a majority have suggested a protective association: the relationships tended to be of moderate strength and sometimes were observed only in subgroups. However, overall, the available evidence suggests according to the Working Group on Physical Activity at the IARC [34] that physical activity may protect against prostate cancer.

To sum up, although the accumulated evidence is not conclusive yet regarding the different dietary and lifestyle factors described above, the observed associations suggest there is a possibility for some preventive measures.

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