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Review

Correlations of dietary patterns with prostate health

Maria Stacewicz-Sapuntzakis[1], Gayatri Borthakur[2], James L. Burns[3], Phyllis E. Bowen[1]

[1] Department of Kinesiology and Nutrition, University of Illinois in Chicago, Chicago IL, USA
[2] Department of Pathology, University of Illinois in Chicago, Chicago IL, USA
[3] Institute for Health Research and Policy, University of Illinois in Chicago, Chicago IL, USA

Both genetic and environmental influences may be involved in etiology of prostate health and prostate cancer. These include ethnic origin, family history, smoking, and diet. Adiposity and excess energy intake are potentially distinct risk factors and positive associations with prostate cancer risk for both were observed among case-control and cohort studies. Some epidemiological studies support an association between dietary fat, particularly saturated or animal fats, and prostate cancer risk. Of these, several suggest reduced risk with low-fat diets high in n-3 fatty acids and increased risk with high-fat diets rich in n-6 fatty acids. Others suggested association with higher meat intake, possibly due to heterocyclic amines and polycyclic aromatic hydrocarbons, produced during grilling or frying. Positive association of prostate cancer risk with dairy intake could involve α-methylacyl-CoA racemase activity (required for β-oxidation of phytanic acid present in dairy products and red meat) or the suppression of vitamin D activity by calcium. Inverse associations were observed with dietary intake of plant foods. These include cereals, soy products, and fruit and vegetable sources of carotenoids. Numerous plant constituents may act synergistically in the prevention and inhibition of prostate disorders. These diet-risk associations may lead to future individualized diet recommendations based upon genetic polymorphisms.

Keywords: Carotenoids / Fatty acids / Obesity / Phytochemicals / Prostate cancer

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1 Introduction

The prevention of prostate diseases is one of the pressing health issues in developed countries. The prostate, a major male accessory gland, is a potential source of serious disorders affecting health and quality of life in older men. The walnut size gland envelops the urethra just below the bladder, and several pathological conditions have a tendency to obstruct the flow of urine, potentially damaging the bladder and kidneys. Prostate disorders include inflammation (prostatitis), benign prostatic hyperplasia (BPH) and prostate cancer. While acute or chronic prostatitis may afflict any adult male, by the age of 70 years more than 40% of men develop an enlarged prostate due to BPH, and by the age of 80 years most will have histological foci of prostatic intraepithelial neoplasia (PIN) or prostate cancer. Premalignant lesions may be found *post mortem* in the third and fourth decades of life in men who had no symptoms of prostate disorders and died of other causes. High prevalence of PIN or preclinical prostate cancer in old men (90% at the age of 90 years) is found in all countries of the world, but in affluent Western societies the disease progresses much faster, resulting in clinical symptoms of cancer and high mortality. Prostate cancer is diagnosed most commonly in Northwestern Europe (Scandinavian countries) and North America, but rarely in East Asia (China, Korea, Japan) [1, 2]. Its incidence has greatly increased over the last 25 years due to the introduction of serum prostate specific antigen (PSA) testing and digital rectal examination. In 2002 there were 679 000 new cases of prostate cancer worldwide and 221 000 deaths resulting from this disease. Incidence and mortality rates are highest among African American men

Correspondence: Dr. Maria Stacewicz-Sapuntzakis, Department of Human Nutrition, UIC m/c 517, 1919 West Taylor St. Chicago, IL 60612, USA
E-mail: msapuntz@uic.edu
Fax: +1-312-413-0319

Abbreviations: **A,** alanine; **ALA**, α-linolenic acid; **AMACR**, α-methylacyl-CoA racemase; **BPH**, benign prostatic hyperplasia; **CI**, confidence interval; **COX-2**, cyclooxygenase-2; **DHA**, docosahexaenoic acid; **EPA**, eicosapentaenoic acid; **IGF**, insulin-like growth factor; **IGFBP**, IGF binding protein; **IL-6**, interleukin-6; **LA**, linoleic acid; **NAT**, N-acryl transferase; **OR**, odds ratio; **PhIP**, 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine; **PIN**, prostatic intraepithelial neoplasia; **PPARγ**, peroxisome poliferator-activated receptor; **PSA**, prostate specific antigen; **RR**, relative risk; **SULT,** sulfotransferase; **V**, valine

and Caribbean men of African descent. Very high rates are also found in some African countries (Uganda, Zimbabwe, South African Republic), implicating a strong genetic predisposition, which is also confirmed by the high risk imparted by family history in all societies. However, the significant increase in incidence of prostate cancer among Chinese and Japanese men after migration to the US [3] indicates the paramount importance of environmental factors. Besides age, ethnic origin, and family history, risk factors for clinically diagnosed prostate cancer may include smoking, lack of exercise, sunlight exposure, environmental contaminants and diet. The long preclinical phase (latency) of prostate cancer implies that diet and nutrition may significantly influence progression of this malignancy at various stages of the male life cycle. An abundance of research on the associations of nutrients and prostate cancer has been summarized in numerous reviews [4 – 12]. This article seeks to integrate recent population, animal and mechanistic studies focused on energy balance, obesity, dietary fats and specific classes of foods, in order to enhance our understanding of their role in the promotion of prostate health, and most particularly the prevention of prostate cancer.

2 Obesity and excess energy intake

Public health messages from the United States National Cancer Institute and private cancer foundations have associated obesity with cancer risk, especially in the face of the obesity pandemic. However, population and animal studies reveal that the dynamics are quite complex for BPH and prostate cancer, with possible protection and risk for various subgroups characterized by cancer stage, age, and family history as a function of excess energy intake or adiposity. Although obesity, generally measured as BMI in population studies, results from chronic positive energy balance at some time in the life of the patient, adiposity itself is likely to exert its own physiological stress independent of chronic or intermittent excess energy intake, making it difficult to separate the effects of these two variables. Furthermore, energy intake is difficult to measure accurately except through the doubly-labeled water technique, which is prohibitively expensive for population studies. Underreporting of energy intake ranges from 10 to 45% compared to doubly-labeled water estimates, with greater underreporting among people with greater adiposity or BMI [13]. Nevertheless, a clearer picture is emerging from the most recent studies.

2.1 Adiposity

Abdominal adiposity, and to a lesser extent, BMI, have been identified as risk factors for BPH and accompanying lower urinary tract symptoms in a number of studies [14 – 20]. Many of these studies find an added link to factors associated with metabolic syndrome, but the association has also been found when overt metabolic syndrome, diabetes and cardiovascular disease have been ruled out [21]. Whether higher circulating energy substrates and anabolic hormones such as insulin support greater prostate volume has not been substantiated.

The association with obesity for prostate cancer is more complicated. Since lower urinary tract symptoms and BPH are common reasons to be screened by PSA testing for prostate cancer, they can have an effect on prostate cancer incidence, although BPH is not generally considered a risk factor for prostate cancer [22].

High BMI is a risk factor for more advanced prostate cancer or cancer fatality [23 – 27]. Even in a relatively lean urban Chinese population, where routine PSA screening is not prevalent, abdominal adiposity (measured as waist to hip circumference ratio) was associated with a 3-fold increased risk for clinically-diagnosed prostate cancer, although BMI was not related to overall risk [28]. Men with higher BMI were more likely to have more severe disease at diagnosis and biochemical or clinical recurrence after prostatectomy or radiation [29 – 32], although poorer outcome was not always found [33]. A large meta-analysis, which included 31 cohort and 25 case-control studies, found a very weak positive association between BMI and all prostate cancer, but the association was much weaker for body weight and central adiposity [34]. Paradoxically, three studies have found reduced risk of prostate cancer, especially for localized cancer, in obese men under 60 or 64 years [35 – 37]. Obesity or overweight at younger ages (by decade <30 years), remembered retrospectively by subjects, reduced the risk for advanced prostate cancer (odds ratio, OR, ranged from 0.40 to 0.59) [38] in one study, but overweight (BMI > 25 kg/m^2) at age 18 years was associated with slightly greater risk for advanced disease (HR = 1.3, confidence interval (CI) 0.94 – 1.7) in another [39]. Weight gain from 18 years to diagnosis was not associated with aggressive or non-aggressive prostate cancer [39], but was associated with fatal disease and not incident disease in another study [37]. These studies do not directly address the hypothesis that positive energy balance-driven alterations in sex hormone patterns during critical male developmental periods affect subsequent prostate cancer risk.

Freedland, Giovannucci, and Platz [40] tried to sort out these apparent contradictions by evaluating three different propositions: (i) obesity increases the risk of aggressive disease, but does not affect the risk of non-aggressive disease, (ii) obesity does not affect the risk of aggressive disease, but decreases the risk of non-aggressive disease, or (iii) obesity increases the risk of aggressive disease, but decreases the risk of non-aggressive disease. By mathematically modeling the effect of differences in PSA screening on the OR for each of their propositions, their results were consistent with position (iii): obesity may reduce the

risk of non-aggressive disease but simultaneously increase the risk of aggressive disease. The model analysis could not take into consideration that high BMI men who have higher prostate volume and risk of BPH [41] may have their cancer detected at an earlier stage, thus reducing their risk for more aggressive cancer. After multivariate adjustment, higher BMI was associated with increased odds of being diagnosed with prostate cancer [25].

2.2 Excess energy intake

Excess energy intake is composed of excess intake of the absolute amounts of fat, carbohydrate or protein, since foods are composed of all three macronutrients. Differences in the macronutrient composition of diets are discussed in the following sections. This section will address the dynamics of positive energy balance and its interplay with adiposity. A meta-analysis of case-control and cohort studies that measured energy intake found a slight positive risk for prostate cancer with higher energy intake (OR = 1.3, 95% CI 1.1 – 1.4) among 14 case-control studies but no association among four cohort studies [42]. Higher energy intake was more positively associated with advanced prostate cancer (OR = 1.6, 95% CI 1.2 – 2.0) in the four case-control studies that differentiated cancer stage, but a single cohort study differentiating cancer stage saw no association [42]. The Baltimore Longitudinal Study of Aging found a positive association with higher energy intakes (OR = 3.79, 95% CI 1.52 – 9.48) and prostate cancer [43]. These studies were limited by lack of control for body size, obesity, physical activity levels and diet reporting bias. A subsequent analysis of prostate cancer in the 46 786 men of the Health Professionals Follow-Up Study cohort did control for these variables and found a relative risk (RR) of 1.38 (95% CI 0.96 – 1.98) for higher energy intakes associated with metastatic or fatal prostate cancer. The risk of high energy intake was greatest for men with lower BMI (<24 kg/m^2, RR = 1.76, 95% CI 0.92 – 3.39), smaller waist size (RR = 1.91, 95% CI 0.83 – 4.36) and who were more physically active (RR = 1.74, 95% CI 0.93 – 8.76), and was restricted to younger men or those with a positive family history of prostate cancer [44]. The authors suggested that the positive energy balance seen in these men, independent of adiposity, may produce a milieu of growth factors that supports cancer cell progression more than cancer cell initiation or promotion. In fact, low energy intake and weight gain were associated with lower serum PSA velocity (a measure of progression) in the Prostate Prevention Trial [45].

2.3 Metabolic rationale

A number of hypotheses have been suggested to explain both the possible protective effect of early obesity and the detrimental effect of obesity on prostate cancer progression, as well as how positive and negative energy balance might modulate tumor growth. Energy restriction has long been known to limit tumor growth in animal studies and prostate cancer models are no exception. When rats were energy-restricted by 20, 30 and 40% of *ad libitum* fed controls immediately after the transplantation of androgen-dependent Dunning R3327-H prostate adenocarcinoma, the resulting tumor size, weight and vascularization were all greatly decreased [46]. While proliferation was unaffected, apoptosis was more than doubled, and vascular endothelial growth factor, required for angiogenesis, was minimally expressed [46]. Further studies with this prostate cancer model, restricting diet by 30% for 16 weeks, were characterized by a contracted stromal compartment, a morphometric picture that indicated a more differentiated and less aggressive phenotype, and androgen receptor staining was reduced in intensity [47]. In rats given testosterone and N-methyl-N-nitrosourea to induce prostate cancer, the 20% diet-restricted rats developed less prostate cancer (65 *vs* 79%) and had a longer prostate cancer-free survival time compared to *ad libitum* fed rats [48]. Transgenic mice (adenocarcinoma mouse prostate TRAMP model) were placed on a 20% diet restriction for 11 and 20 weeks beginning at seven weeks of age. Compared to *ad libitum* fed mice, all prostate lobes showed a reduction in lesion severity [49]. When the experiment was repeated with 20% diet restriction starting after 20 weeks of age, the effect was less pronounced. Although serum insulin-like growth factor-1 (IGF-1) decreased with age in both diet restricted and unrestricted mice, the decrement was greater in the diet restricted animals but only during the final weeks of the study [50]. The mechanist rationale behind these studies is that energy restriction, in early life, produces adjustments in the hormonal and growth factor environment which may protect against subsequent prostate carcinogenesis. However, the Netherlands Cohort Study group found no evidence that energy restriction in early life decreases prostate cancer risk in later life [51]. In an effort to determine whether changes in dietary energy excess or the accompanying changes in body weight and adiposity were the major influences on prostate carcinogenesis, the ambient temperature was raised close to the TRAMP mouse thermoneutral zone, while the control animals were kept at 5°C lower and food intake remained similar through pair-feeding. The mice kept at higher temperature were heavier, had greater body fat, higher serum leptin and lower adiponectin concentrations, and a greater frequency of prostatic carcinoma [52]. The authors concluded it was adiposity and body mass, rather than dietary energy excess and the accompanying hormonal changes, that provided the carcinogenic environment.

Excess energy intake is difficult to achieve in rodent models, but high-fat diets produce modestly higher energy intakes and have been used as a model for excess energy intake. Again, these studies cannot control for accompanying changes in body mass and composition. Rats fed a high-

fat diet after weaning, resulting in higher energy intake over the first four weeks compared to low-fat diet controls, had higher prostate mRNA expression for 5α-reductase-2 at two weeks of age (but not at four and ten weeks). It was accompanied by an increase in plasma dihydrotestosterone, a major prostate growth stimulator [53]. 5α-Reductase inhibitors are an important part of therapeutic strategies against prostate cancer. Prostate weight of the high fat fed animals was not increased over their low fat controls until ten weeks of age [53].

These animal studies indicate that differences in energy intake or body mass or adiposity at critical periods in prostate development may modulate hormones that directly affect prostate growth and architecture. The abundance of high energy substrates due to excess intake may be associated with higher circulating insulin and IGF-1 levels [54, 55] or lower IGF binding protein (IGFBP)-1 [56], but the association with obesity is not straightforward and is age dependent [57]. Higher plasma IGF-1 has been associated in a number of studies with higher risk for prostate cancer [58] but its use as an independent screening marker for prostate cancer is controversial [59]. Increased adiposity leads to changes in the secretion pattern of a number of adipokines, including a decrease in adiponectin (reduces prostate cell growth in culture), and increases in interleukin-6 (IL-6), an inflammatory factor, and leptin, both of which increase prostate cell growth in culture [60]. Both early prostate development and cancer cell development are under androgenic steroid control, which is strongly modulated by energy supply [61, 62]. However, the progressing prostate tumors escape androgen control, become less differentiated and secrete their own growth factors such as IGF-1 and vascular endothelial growth factor [63]. This adipokine milieu, supported by increased adiposity, may become more important as a risk for advanced stage cancer and mortality. To assess whether these factors have any role in late stage cancer, in a nested case-control study 125 cases with high grade disease (Gleason sum > 7) were selected from the San Antonio Center for Biomarkers of Risk of Prostate Cohort Study. Neither BMI, plasma leptin, nor IL-6 were associated with high grade disease [64].

Despite a complicated picture emerging from these recent studies of the consequences of excessive energy intake and obesity for the development of advanced prostate cancer, it seems prudent to advise energy restriction to maintain an ideal body weight at each stage of life.

3 Dietary fat

Total dietary fat intake, particularly from animal sources, may be directly associated with increasing the risk for developing prostate cancer. Numerous reports suggest the direct association between *per capita* consumption of total fat and prostate cancer mortality [65 – 68]. Most of the available data regarding the association of dietary fat and cancer in humans have come from cohort and case-control studies with various limitations in their methodologies. A comprehensive case-control study among African-Americans, European-Americans and Asian-Americans observed an increase in the risk with greater total fat intake across all ethnic groups [69]. About 10 – 15% of the difference in prostate cancer incidence among these ethnicities was attributed to differences in saturated fat intake [70]. The Seventh-Day Adventists study provides more evidence that high animal fat consumption increases the risk of prostate cancer, particularly fatal cancers [23, 71]. Randomized trials studying the effect of a single dietary factor as a chemopreventive agent were not very consistent [72 – 74], A few cohort studies showed no significant association between fat consumption and development of human prostate cancer [75, 76], but a majority support an association between dietary fat, particularly saturated or animal fats, and risk of prostate cancer [77 – 80].

The influence of dietary fat on prostate cancer may be due to particular fatty acids. There has been a search for a potential association between specific type of fat and prostate cancer risk, but results have not been consistent. Several studies indicate that low-fat diets high in n-3 fatty acids may reduce the development and progression of prostate cancer, and that high-fat diets rich in n-6 fatty acids may promote the growth of prostate cancer cells. The dietary intake of linoleic acid (LA, n-6 fatty acid) is very high in the typical Western diet. In the Far East, the intake level is 0.8% of energy as linoleate, while in the US linoleate constitutes 8.9% of energy [81]. LA is responsible for exerting stimulatory effects on inflammatory agents such as prostaglandins and leukotrienes. These proinflammatory fatty acid metabolites can also promote tumor growth. Long chain n-3 PUFA of marine origin may modify the biosynthesis of prostaglandins and eicosanoids from arachidonic acid (n-6 PUFA) through competitive inhibition of cyclooxygenase and lipoxygenase pathways [82]. The cyclooxygenase-2 (COX-2) enzyme plays an important role in the process of prostate carcinogenesis. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are the major n-3 fatty acids in marine fish oil. Research on n-3 fatty acids in relation to coronary heart disease has focused on the roles of EPA and DHA as anti-inflammatory agents. Since n-3 PUFA act as competitive inhibitor of arachidonic acid by substituting for arachidonic acid in the cell membrane and competing for COX enzyme, much interest in recent years involved possible effects of n-3 PUFA in prostate carcinogenesis. One of the earliest randomized trials observed that a Mediterranean diet low in total fat, saturated fat and n-6 fatty acids, but rich in n-3 fatty acids, oleic acid, fiber, antioxidants and vitamins of the B group, may protect against many forms of cancer [83]. A preliminary trial in men with prostate cancer, consuming a low-fat diet supplemented with fish oil rich in n-3 fatty acids for three months, showed

a significant increase in the n-3/n-6 fatty acid ratio in plasma and adipose tissue and a decrease in COX-2 enzyme in the prostate biopsy [84]. Large population based case-control and prospective cohort studies showed an inverse association between intake of fatty fish and prostate cancer risk [85 – 89]. One of these [86] reported that men with high levels of EPA and DHA in their erythrocyte membranes had a 40% lower risk of prostate cancer than those with low levels. Men consuming moderate to large amounts of fish had only one-third to one-half the risk of prostate cancer as those who did not consume any fish. Eating fish more than three times per week was associated with a reduced rate of prostate cancer, and the strongest association was for metastatic cancer (multivariate RR = 0.56; 95% CI, 0.37 – 0.86) compared with infrequent consumption and intakes of less than twice per month.

However, α-LA (ALA) is the major n-3 fatty acid that has been studied in relation to prostate cancer, as there is some evidence that ALA is positively associated with prostate cancer risk. ALA, the plant-based n-3 fatty acid with 18 carbons and 3 double bonds, is the precursor for EPA and DHA. Unlike these highly unsaturated fatty acids, high intake of ALA has been shown to increase prostate cancer risk. This variable effect of different types of n-3 fatty acids may be due to their different dietary sources. Dietary ALA occurs mainly in plants and vegetable oils, but also to some extent in meat products, because animals obtain it from the food cycle. In the United States, important sources of ALA are margarine, butter, mayonnaise, oil-and-vinegar-based and creamy salad dressings, beef, pork, lamb [89]. Several studies report strong positive associations of ALA and prostate cancer risk. In 1993, the Health Professionals Follow-Up Study [89] suggested that saturated fat, monounsaturated fat and ALA, but not LA, were associated with advanced prostate cancer risk. When all these fatty acids were modeled simultaneously, only the association with ALA persisted. A similar result was reported by another Harvard study in 1994 [90]. Serum analysis of ALA was done for 120 men from the Physicians' Health Study, who developed prostate cancer. The results were compared with those who remained free of the disease. Although ALA levels were correlated with intake of red meat and butter, the association of ALA with prostate cancer was greater among men with low LA and reduced meat intake. A recent study, analyzing ALA levels in prostate tissue and leukocytes in men with prostate cancer and BPH, reported that the ALA concentration was significantly higher in prostate tissue than in leukocytes in men with prostate cancer, while these levels were similar in men with BPH [91]. A case-control study measured erythrocyte membrane n-3 and n-6 fatty acid levels in 67 incident prostate cancer cases and 156 population-based controls. The results indicated that LA, total n-6 fatty acids and ALA were positively associated with increased risk of prostate cancer [92]. The highest levels of ALA intake were linked to a 3 – 4-fold increase in prostate cancer risk, whereas highest levels of serum ALA correlated with 2.6-fold greater risk of prostate cancer [93]. However, there are a few studies reporting that ALA has no association [94, 95], or that it is linked to decreased risk of prostate cancer [75].

In order to answer the question whether over-consumption of dietary fat is associated with the development and progression of prostate cancer, several animal studies have been conducted. Reduced dietary fat intake delayed the progression of prostate cancer to the hormone-independent stage and thereby significantly improved survival in xenografted severely immunodeficient mice [96]. Similarly, reduction of dietary fat slowed the growth of tumors established from human prostatic adenocarcinoma cells in a murine xenograft model [97]. While other studies have found no relationship between the growth of prostate tumor and modification in dietary fat, a reduction in the growth of prostate adenocarcinoma was reported on a fat free diet [98 – 100].

The mechanism linking dietary fat and increased prostate carcinogenesis is far from clear. It is hypothesized that the fat-cancer association may involve the effect of dietary fat on hormonal levels, IGF-1, and free radical damage. A weak association has been reported between fat and testosterone level [101]. IGF-1 hormone and the protein IGFBP-3 have been shown to be predictors for advanced stage prostate cancer [102, 103]. A recent feeding experiment in men demonstrated that a low fat diet and/or intensive exercise modifies serum hormones in such a way that it reduces growth and induces apoptosis in LNCaP prostate tumor cells *in vitro*. These effects are mediated through modulation of the insulin/IGF-1 pathway, as shown by low serum levels of insulin and IGF-1 but higher level of IGFBP-1 in low dietary fat groups [96, 104]. An investigation with single and combined n-6 and n-3 fatty acids showed that, except for oleic acid, arachidonic acid and LA, which had very little effect on the cells, an increase in cell mortality was observed at physiological concentrations of EPA, ALA and γ-LA. However, combining these fatty acids at physiological concentrations did not show a similar effect [105]. PUFA attenuate prostate carcinogenesis via *in vivo* generation of 15-lipoxygenase metabolites [106]. There are indications that over-expression of COX-2 enzymes, nuclear factor-kappaB (NF-κB), nuclear receptors, such as peroxisome proliferator-activated receptor γ (PPARγ), retinoic acid receptor (RAR) and retinoid X receptor (RXR), have an important role in prostate carcinogenesis. It has been shown that treatment of prostate cancer cell lines, such as LNCaP, DU-145 and PC-3, with n-3 fatty acids, like DHA, leads to modulation of expression of these molecular parameters, thus inducing cell growth inhibition and apoptosis. This modulation was more pronounced when DHA was combined with COX-2 inhibitor celecoxib at low concentrations [107]. The inhibition of arachidonic acid-derived eicosanoid synthesis, regulation of transcription

factor activity, such as PPARγ, regulation of gene expression for this receptor, and altered estrogen metabolism are the potential mechanisms by which n-3 long chain PUFA may inhibit cancer development at the early stages.

4 Meat intake

Results of epidemiological studies, though not consistent, are generally suggestive of a greater risk of prostate cancer with higher meat intake. Ecological studies [108, 109] have reported positive relationships. A review summarizing results of 14 case-control and eight cohort studies, found that most of them showed risk ratios of 1.2 or greater [110]. Of the four case-control and four cohort studies distinguishing red meat, only one of the case-control studies failed to show a positive risk ratio of 1.2 or more. In contrast, a more recent review, tabulating results of cohort studies, found less convincing evidence, possibly due to more stringent inclusion criteria [9]. Relative risk greater than 1.2 was found in three of the seven studies examining overall meat intake, and in four of the seven cohort studies assessing some measure of red meat intake.

Among case-control studies, evidence for increased risk associated with well-done meat consumption has been seen among US males (OR = 1.7, 95%CI 1.2 – 2.4) [111], whereas among Italian males nonsignificantly increased risks were observed with intake of poultry (OR = 1.3, 95%CI 1.0 – 1.6), and fish (OR = 1.3, 95%CI 1.0 – 1.7) [112], but none with processed meat or red meat [113]. Four recent cohort studies investigated meat intake and prostate cancer risk or prostate cancer progression. Among a cohort of US men in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial, no association was observed for total, red, or white meat intake with prostate cancer risk [114], though a higher risk was seen with intake of very well-done meat (RR = 1.42, 95%CI 1.05 – 1.92). Another study found associations with red meat intake among younger (<65 year old) males and with processed meat intake among older (at least 65 year old) males [115]. Among a cohort of males enrolled in the Cancer Prevention Study II no association of meat intake with incident prostate cancer risk was seen among European-Americans, but a positive association attributable to cooked processed meats, was observed among African-Americans [116]. No association of post-diagnosis red meat intake with prostate cancer progression was seen among men with prostate cancer in the Health Professionals Follow-up Study [117]. Studies showing an association with meat intake appear more likely to consider how well-done meat was cooked [111, 114, 116], in contrast to studies showing no association and no mention of cooking degree [112, 117].

Three case-control studies and one cohort study have examined the risk of BPH associated with meat intake. With so few studies of varying methodology, results vary considerably and must be interpreted cautiously. Among Italian males, an increased risk of BPH was seen with higher poultry intake and decreased risk among those in the highest quintile of red meat intake [118], but among Greek males no association of combined meat, fish and egg intake with BPH risk was found [119]. In a cohort of Japanese-American men, an increased risk was observed with higher beef intake [120] and among Japanese men, a nonsignificantly increased risk was suggested for daily meat consumption [121].

Several possible explanations have been proposed for the putative association between meat intake and prostate cancer risk [110, 122]. The association may be due to the positive correlation of meat with fat intake. Among the fatty acids provided by meat, phytanic acid has been associated with prostate cancer risk [123]. Otherwise, meat intake may be negatively correlated with the intake of plant foods with their potential anticarcinogenic properties. Another possibility is that the zinc provided by red meat enhances the synthesis of androgen hormones, which may have adverse effects on prostate cancer development. Grilling or frying of meats may produce mutagenic compounds such as heterocyclic amines, produced from pyrolysis of amino acids and other food constituents, or polycyclic aromatic hydrocarbons, produced by pyrolysis of fats when grilling over coals. The polycyclic aromatic hydrocarbon, benzo[*a*]pyrene, has been shown to cause DNA damage in prostate tissue culture [124].

Most of the recent interest regarding prostate cancer and meat intake has focused on heterocyclic amines. Though the tumorigenicity of extracts from broiled horsemeat was first shown in 1939 [125], further work came later with the demonstration of mutagenicity of compounds from broiled meats and fish in bacterial culture [126] and the subsequent isolation of the heterocyclic amines [127]. Shirai *et al.* [128] showed that the heterocyclic amine, 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (PhIP), produced prostate cancer when fed to rats. Daily heterocyclic amine intake among the US population is estimated to range from 11 to 20 ng/kg of body weight [129], with PhIP as the major contributor, comprising approximately 70% of total mean heterocyclic amine intake. African-American males show the greatest intake of heterocyclic amines. Among cooking methods, pan-frying contributes most to exposure and among types of meat, chicken is the greatest contributor [129], though no consistent association of chicken intake with prostate cancer has been observed.

Heterocyclic amines are activated by cytochrome P450 (CYP) enzymes [130]. PhIP is hydroxylated in the liver by CYP1A2 to form *N*-hydroxy-PhIP, which may bind to DNA, though further esterification brings about greater reactivity [131]. The carcinogens can be also activated in prostate, as shown in experiments with the tissue obtained from surgery to alleviate BPH [132]. Cytochrome P450 enzymes were expressed in these tissues, and mutagenic

DNA adducts were isolated after incubation with PhIP or N-hydroxy-PhIP. Hydroxylated heterocyclic amines undergo N-acetylation by the acetyltransferases, NAT1 and NAT2, or sulfation by the sulfotransferase (SULT) [131]. The reactive products of PhIP form DNA adducts with guanine [131]. Transcripts of NAT1, NAT2 and SULT have been found in human prostate tissue [133, 134]. An association between grilled meat intake and PhIP-DNA adducts in tumor cells was recently shown in prostatectomy specimens [135]. Detoxification occurs through the action of glutathione S-transferase, with human glutathione S-transferase A1 acting on *N*-acetoxy-PhIP [130]. Glucuronate conjugates are formed in the liver from *N*-hydroxy-PhIP [131] and excreted in urine.

The association between meat intake and prostate cancer risk observed in epidemiological studies has lead to many further investigations. Coffey [136] offered some interesting thoughts regarding this association. Humans and dogs are the only known species with significant prostate cancer incidence. Since humans first enlisted the help of dogs in hunting about 12 000 years ago, both species together experienced substantial changes in diet, including higher meat intake and frequent consumption of cooked meat by dogs. Subsequent introduction of herding and agriculture provided a greater supply of meat and excess energy to both species.

5 Dairy foods

Epidemiological reports suggest that a diet high in dairy products increases the risk of prostate cancer. Although saturated fat is an obvious factor to consider in this regard, available evidence suggests that other factors may also be important. Calcium is another component of milk and milk products that may be associated with prostate cancer risk. Calcium increases this risk by suppressing $1,25(OH)_2D_3$ (an active vitamin D metabolite) levels [137], which has antiproliferative, proapoptotic and cell differentiation effects on human cancer cell lines [138 – 140]. Therefore a diet high in calcium and low in vitamin D levels may be associated with increased prostate cancer risk. It is well known that advanced prostate cancer shows a tendency to invade the bone and form osteoblastic tumors [141], while vitamin D_3 activates osteoclasts causing bone resorption. However, studies investigating the potential role of calcium in prostate carcinogenesis are very limited. A recent prospective cohort study in France reported that the harmful effect of dairy products on prostate carcinogenesis was largely related to calcium. However, the higher risk of prostate cancer with increase in yogurt consumption seems to be independent of calcium [142]. Another study reported that consumption of whole yogurt was associated with decreased prostate cancer risk [88]. In a summary of results from ten cohort and eleven case-control studies, it was observed that the relationship of cancer risk with calcium intake was significant in four studies. Another four studies had risk estimates around 1, seven reported risk estimates above 1 and only one study reported risk estimates below 1. An association between calcium and prostate cancer has been mainly observed for more advanced disease or very high intakes (above 2000 mg/day). Similarly, 14 studies investigated the effect of vitamin D on prostate carcinogenesis. Four of them had non-significant direct relations, five had inverse relations, none significant, and four reported risk estimates around 1.0 [143]. In 2004, a case-control study reported a direct association between milk and dairy product consumption and prostate cancer risk, but no relation with cheese [112]. After one year the same group, reporting the results from dietary intake analysis, observed no material association of dietary calcium, vitamin D or phosphorus with prostate cancer risk [143]. This discrepancy may be due to many reasons. Calcium intakes from dairy sources and the use of calcium supplements vary among different populations. Dietary intake of vitamin D may not be reflected in circulating levels, since it is also synthesized in the skin by ultraviolet light. Prostate cancer mortality rates in 71 countries around the world were strongly correlated with increased latitude from the equator and there was an even more significant negative association with ultraviolet index, suggesting a protective role of sunlight exposure [144]. Calcium and phosphorus modulate $1,25(OH)_2D_3$ levels. When dietary calcium is very low, the reduced plasma calcium levels increase the conversion rate of vitamin D to $1,25(OH)_2D_3$, which in turn enhances the intestinal absorption of calcium. Similarly, low blood levels of phosphorus increase plasma $1,25(OH)_2D_3$. Thus a hypothesis has been proposed that a diet low in calcium and phosphorus increases circulating levels of $1,25(OH)_2D_3$ and consequently decreases the risk of prostate cancer [145].

Recently much emphasis has been placed on the α-methylacyl-CoA racemase (AMACR) gene and its overexpression in high-grade PIN and in a majority of prostate cancer samples. AMACR is required for the β-oxidation of branched chain fatty acids, such as phytanic acid and its α-oxidation product, pristanic acid, both of which are obtained from dietary intake of dairy products and red meat. The observed association of prostate cancer risk and consumption of dairy products and red meat suggests that the intake of phytanic acid may be associated with prostate cancer risk. The results of a case-control study of 104 prostate cancer patients and controls, conducted in North Carolina, indicate a significant association of serum phytanic acid and prostate cancer risk [123]. The negligible expression of AMACR in normal prostatic epithelium contrasted with its overexpression in prostate cancer, and its importance in the metabolism of phytanic acid prompted many *in vitro* studies to explore the factors regulating this enzyme. One such study on prostate cancer cell lines reported that AMACR was significantly up-regulated in LNCaP cells,

compared to androgen independent DU-145 and PC-3 cells, and that the addition of phytanic acid and pristanic acid to cell growth media resulted in a marked increase in AMACR expression at the protein level [146]. Another study of prostate needle biopsies reported that those containing foci of prostate cancer exhibited 6.6 fold higher AMACR activity than benign tissues [147].

6 Plant based foods

6.1 Cereals

Cereals constitute the bulk of plant-derived food products. In a study of 32 countries with predominantly white populations there was an inverse correlation between average cereal intake (total calories) and prostate cancer mortality [148]. Another ecological study [144] found a similar strong correlation, particularly for the consumption of rice ($R = -0.60$, $p = 0.0001$) in 71 countries worldwide. It does not seem to stem from general high carbohydrate intake, because consumption of sugar is associated with increased prostate cancer mortality ($R = 0.71$, $p = 0.0001$). A diet based on complex carbohydrates generates less IGF-1 than high intake of fat and protein [149]. Whole grain cereals also contain potentially anticarcinogenic nutrients, like vitamin E and lignans, which possess antioxidant and/or phytoestrogenic properties. Rye bran and its extracts, rich in resorcinol compounds, were fed to nude mice injected with human LNCaP prostate adenocarcinoma cells [150]. The treated animals developed fewer tumors, of smaller size, and secreting less PSA than the control group, due to increased apoptotic effect. Interestingly, rye bread is a staple in Eastern and Central Europe, where prostate cancer is less common [4] than in Western and Northern Europe. This trend is preserved in immigrants to Canada and Australia, who maintain their traditional diet.

6.2 Soy products

Soy products are an important source of protein in East Asian countries with low rates of prostate cancer. A meta-analysis of eight recent epidemiological studies from North America, China and Japan [151] produced a summary risk estimate of 0.70 (95% CI 0.59 – 0.89, $p = 0.001$), indicating a significant protective effect. Worldwide ecological studies [152, 153] correlated lower mortality from prostate cancer with higher consumption of soy *per capita*. Soy contains high levels of isoflavones (daidzein, genistein), which have estrogen-like properties in some animals, and therefore are called phytoestrogens. Japanese men with higher serum isoflavones had a lower incidence of prostate cancer [154]. In a large population-based prospective study of 43 500 Japanese men, high soy food and isoflavone intake was associated with a 50% decrease in the risk of localized prostate cancer for 60 – 74 year old participants [155]. Some studies found lower levels of circulating androgens in men consuming large amounts of soy products [156], and detected such a decrease even after a single soy meal [157], while others did not observe such effect [158]. Dietary genistein down-regulated expression of androgen and estrogen receptors in rat prostate [159], and soy isoflavones inhibited the growth of transplanted human prostate adenocarcinoma in nude mice, by reducing angiogenesis and increasing apoptosis in the tumors [150, 160]. Numerous experiments with prostate cancer cell lines *in vitro* indicate a suppression of PSA production, inhibition of enzymes involved in sex-hormone metabolism (5α-reductase, aromatase) by soy polyphenols, all promising a possible role in prevention of prostate cancer development [7].

6.3 Total fruits and vegetables

There is inconsistency in the epidemiological studies trying to correlate the intake of fruits and vegetables with prostate cancer incidence and mortality, depending on the investigated population, the methods of estimating the dietary intake, and the statistical evaluation of accumulated data. A recent study of seven European countries did not find any association between total fruit consumption, total vegetables consumption, combined fruit and vegetables, and the incidence of prostate cancer in each of the countries, and in all countries combined [161]. This prospective study of 130 544 men, with 1104 cases registered five years after baseline intake estimate, with a wide range of plant food intake and rates of prostate cancer incidence, did find that the highest median consumption of fruits and vegetables in Spain coincided with low prostate cancer incidence, and the lowest intake in Sweden was accompanied by the highest incidence ratio of this malignancy. Similarly, fruit and vegetable intake had no association with cancer risk in Hawaii, when 452 cases were compared to 899 age matched controls [162], but a high intake of papaya was observed among older cases (> 70 years old). Prospective data from the National Health and Nutrition Examination Survey Epidemiological Follow-up Study cohort (NHANES and NHEFS) showed that prostate cancer risk was not associated with vegetable and fruit intake, but intermediate intake of vegetables and fruits tended to increase the risk of prostate cancer (RR = 1.5, 95% CI 0.9 – 2.3). When fruits and vegetables were examined separately, there was no association for vegetables, but a slightly increased risk at the intermediate level of fruit intake [163]. Dietary intervention by intensive counseling to consume a low-fat, high fruit and vegetable diet failed to slow the increase of serum PSA concentrations in healthy subjects over time in the Polyp Prevention Trial [164, 165]. Although the intervention group reduced their fat intake by 15%, and increased fruit and vegetable intake by 2.25 servings per day compared to control group, the incidence of prostate cancer was similar in both groups after four years.

However, many studies indicate just the opposite relationship between prostate cancer and plant-based diets which included large amounts of fruits and vegetables. An investigation of total fruit and vegetable intake of histologically confirmed prostate cancer cases and their matched controls in India (n = 390 and 780, respectively) found a highly significant linear trend for a protective effect with increased consumption [166]. As vegetarian food is a vital part of Indian culture, the lowest tertile consumed less than 2 kg of fruit and vegetables per week, and the highest tertile more than 3 kg/week. This high level of intake produced a very low OR for developing prostate cancer (OR = 0.4, 95% CI 0.3 – 0.6). Possibly the studies conducted in Western societies are limited to relatively low levels of intake, which do not reach an optimal range and therefore are inconclusive. However, a similar case-control study in western New York [167] found reduced risk in the highest quartile of total vegetable intake (OR = 0.53, 95% CI 0.36 – 0.79), and an Australian study [168] also observed an inverse association of prostate cancer incidence with total vegetable consumption (OR = 0.7 for the highest tertile, 95% CI 0.5 – 1.0, $p_{trend} = 0.04$). Fruit intake was found to be protective against BPH in a case-control study of 184 patients and 246 controls in Greece [119].

6.3.1 Carotenoids

Many deeply colored fruits and vegetables are rich in carotenoids, fat soluble plant pigments possessing antioxidant properties. Some of them are converted to vitamin A compounds in human tissues by the widely expressed carotene oxygenase enzymes. Carotenoids are well absorbed by human intestinal epithelium and accumulate in many tissues, including prostate, where they may exert anticancer effects. A multiethnic case-control study identified through population-based tumor registries in US, British Columbia and Canada, found that yellow-orange vegetable consumption reduced the risk of prostate cancer, especially for advanced cases [169]. Two individual vegetables, corn and carrots, were especially effective. Corn is the richest source of lutein and zeaxanthin, and carrots contain the highest amounts of α-carotene and β-carotene among commonly consumed foods in these countries. When the risk of prostate cancer was calculated according to quartiles of individual dietary carotenoid intake, all major carotenoids seemed to be protective [167] in the above mentioned western New York study. Similar results were obtained in China [170], where tomato, watermelon, pumpkin, spinach and citrus intakes were inversely associated with the risk of prostate cancer, and all major dietary carotenoids produced very significant dose response relationships. Tomato and watermelon are the main sources of lycopene, pumpkin contains plenty of α-carotene and β-carotene, spinach is a good source of both lutein and β-carotene, while citrus fruits, especially mandarin oranges, deliver β-cryptoxanthin and lutein.

The growing popularity of tomato products in the Western diet causes lycopene to be a predominant carotenoid in serum and induced many researchers to study its possible interaction with prostate cancer. The most thoroughly investigated population of male health professionals in the US, the Health Professionals Follow-up Study, found inverse associations between the intake of lycopene or tomato products and the risk of prostate cancer in subsequent questionnaires mailed to entire cohort of about 50 000, whereas no other fruit or vegetable or total fruits and vegetable consumption was associated with lower risk [171, 172]. Tomato sauce, a good source of bioavailable lycopene, was associated with a greater reduction in prostate cancer risk than calculated lycopene intake from all sources. Consumption of more than two servings per week, contrasted with less than one serving per month, resulted in RR of 0.77 (95% CI 0.66 – 0.90). The inverse association with lycopene was confirmed by case-control studies of plasma carotenoids, nested within the same cohort, especially for aggressive prostate cancer [173], and for older (>65 years of age) participants without a family history of prostate cancer [174]. Among younger men, higher plasma levels of β-carotene were associated with decreased prostate cancer risk.

A small intervention study was conducted with 32 patients diagnosed with adenocarcinoma of prostate, who agreed to consume pasta with tomato sauce every day for three weeks preceeding their prostatectomy. Their blood lycopene doubled and their prostate lycopene content tripled during this short period, with significant decrease in blood PSA and oxidative DNA damage in leukocytes and prostate tissues [175]. Histological examination of their prostate tissue revealed increased apoptosis in carcinoma regions [176].

However, it could be argued that carotenoids are simply excellent markers of the intake of particular fruits or vegetables, but by themselves do not exert any special effect on the risk of prostate cancer. In a study of rat prostate cancer induced with N-methyl-N-nitroso-urea and testosterone, tomato powder added to diet was much more effective than supplemental lycopene in beadlets, prolonging survival and reducing mortality [48]. Nevertheless, other studies of rats injected with cancer cells into prostate (MatLyLu Dunning model) indicate that a lycopene-augumented diet may increase tumor necrosis rates by downregulation of genes involved in inflammatory signaling (IGF-1 and IL-6), generation of reactive oxygen species, and androgen expression [177]. A similar lycopene-enriched diet did not prevent normal prostate development in young healthy rats, but modulated the expression of genes important to prostate health by decreasing androgen activation and inflammatory signaling [178]. Oral supplementation of young rats with lycopene, phytofluene (another tomato carotenoid, precursor of lycopene) or a diet containing 10% tomato powder produced a very significant decrease in serum testosterone

after only four days of treatment [179]. Cell culture studies show that lycopene may increase apoptosis and decrease proliferation by arresting cell cycle of various human prostate cell lines [180, 181].

6.3.2 Other phytochemicals

Beside soy isoflavones and tomato carotenoids, many other plant constituents have shown promise for the prevention and inhibition of prostate diseases. Most of the studies were conducted on prostate cancer cell lines, but the impulse often came from epidemiological studies, that indicated a decreased risk of cancer for subjects consuming larger amounts of particular plant food. Among the most protective vegetables in predominantly white populations are onions [148], which also seem to significantly decrease prostate cancer mortality worldwide [144]. Case-control studies [168, 182] indicated reduced risk of prostate cancer with increased consumption of *Allium* vegetables (onions, garlic, leeks), possibly due to their organosulfur compounds which inhibit growth of human cancer cells *in vitro*, including prostate cancer cell lines [183]. In a large data set from Italian case-control studies, the multivariate ORs for prostate cancer were 0.29 and 0.81, respectively, for the highest categories of onion and garlic consumption compared with the lowest ($p_{trend} = 0.05$) [184].

Another group of protective vegetables are *Cruciferae* (cabbage, broccoli, cauliflower, brussels sprouts), which were inversely related to prostate cancer risk in a multiethnic case-control study of Hawaii, California, and Canada [169] (OR = 0.61, $p_{trend} = 0.006$), which included white, black, Japanese and Chinese subjects. A moderate inverse association was found in the large longitudinal US Health Professionals Follow-up Study (since 1986) for younger men, with confined prostate cancer, who had a consistently high intake of cruciferous vegetables for ten years prior to 1986 [185]. Cruciferous vegetables contain isothiocyanate compounds, with sulphoraphane being the most predominant and widely investigated in cancer research. It inhibited growth of DU-145 prostate cancer cells *in vitro* by retarding cell cycle progression and activation of apoptosis [186].

Hot chili peppers contain a potent irritant capsaicin, which has a profound inhibiting effect on the growth of three prostate cancer cell lines *in vitro* [187], arresting the cell cycle, inducing apoptosis, and blocking dihydrotestosterone-induced PSA production. In an animal model (nude mice) human prostatic cancer xenografts resulted in significantly smaller tumors in capsaicin-treated animals. The oral treatment started after the injection of PC-3 cells in animal flanks.

Similar experiments were carried out with grape seed extract [188], containing procyanidins, which are also present in red wine. Nude mice injected with DU-145 cells and treated with daily doses of grape seed extract developed much smaller tumors, showing increased apoptosis in histological examination and reduced angiogenesis, as well as the inhibition of IGF-1 signaling by increasing IGFBP levels.

Although beer consumption was found to be rather positively associated with the risk of prostate cancer mortality [144], hops used in brewing are a source of flavonoids (xanthohumol), which, *in vitro,* inhibit proliferation of prostate epithelial cells, both benign hyperplastic (BHP-1) and malignant [189, 190]. Another flavonoid present in citrus fruits, naringenin, stimulates DNA repair in prostate cancer cells *in vitro* [191], following oxidative damage.

Recently, pomegranate juice was reported to slow the PSA rise in prostate cancer patients after surgery or radiotherapy [192], which may indicate modulation of disease progression. Daily pomegranate juice consumption for nine months decreased serum lipid peroxidation in those patients, and their serum had an increased apoptotic and antiproliferative effect on prostate cancer cell line (LNCaP) *in vitro*. Pomegranate juice has a high content of polyphenols, with the most abundant being punicalagin. Pomegranate extracts were found to inhibit *in vitro* proliferation of LNCaP and other prostate cell lines (PC-3, DU-145), and to reduce xenograft tumor growth in athymic mice [193, 194]. The extracts of common berries (blackberry, raspberry, blueberry, cranberry and strawberry) also had antiproliferative effects on LNCaP cell lines [195], possibly due to their high content of various phenolic compounds.

Certain medicinal plants, used by native healers, were found to have high concentrations of active phytochemicals, which also occur in many commonly consumed fruits and vegetables. Turmeric, a popular spice, food colorant, and herbal medicine in Asia, contains bright yellow phenolic compound, curcumin, which induces apoptosis and supresses proliferation of human prostate cancer cell line PC-3, and also inhibits growth of PC-3 xenografts in nude mice [196]. The tumor suppressing activity of curcumin seems to be related to its down-regulation of oncogene MDM2, and it enhances the antitumor activity of radiation and of chemotheurapeutic agent, gemcitabine. Lupeol, a pentacyclic triterpene, is present in many fruits, among them mangoes, strawberries, grapes, figs, olives and tomatoes. When tested on human prostate cell lines, lupeol decreased cancer cell viability and caused apoptosis, but had no effect on normal epithelial cells. It was also an effective inhibitor of fast growing xenograft tumors in nude mice, with decreased serum PSA levels [197]. The presence and synergistic action of many agents in plant food may have a considerable preventive effect on the development and progression of prostate diseases.

6.4 Tea

Tea is a very popular beverage, particularly in East Asia, where the incidence of prostate cancer is the lowest in the world (only 1 – 2 cases per 100 000 in China). Tea leaves contain a plethora of polyphenolic compounds with anti-

oxidant properties. Green tea is particularly rich in catechins (such as epigallocatechin-3-gallate), while black tea contains thearubigens, produced from catechins during the fermentation process. Significant negative associations for tea drinking and risk of prostate cancer were found in a few epidemiological studies, and at least two case-control studies, in Canada and China. Green tea seems to have stronger effect than black tea, especially when consumed in large quantity over a lifetime (OR = 0.28, 95% CI 0.17 – 0.47 for drinking green tea, OR = 0.12, CI 0.06 – 0.26 for over 40 years of drinking tea, OR = 0.09, CI 0.04 – 0.21 for consumption of more than 1.5 kg of tea leaves per year) [198]. Short clinical trials with green tea were not conclusive, but several studies using animal tumor models and human prostate cell cultures yielded promising results [199]. Green tea polyphenols downregulated the expression of androgen receptor in LNCaP prostate carcinoma cells, reduced their PSA production and increased apoptosis. The proliferation of other prostate cell lines, DU-145 and PC-3, was also inhibited by green tea catechins. The growth of prostate tumor xenografts in mouse models was reduced due to the induction of apoptosis and decrease in angiogenesis by green and black tea extracts and their constituents.

7 Minerals: Selenium and zinc

The role of selenium for prevention of prostate cancer is currently under intensive investigation in at least four clinical trials (NutraIngredients 2006, http://www.nutraingredients-usa.com/news/ng.asp?id=67480.). Some ecological studies suggest lower mortality from prostate cancer in areas with a high soil content of selenium, where both plant and animal food products accumulate more of this element. Seafood is also a good source of selenium [200], but by far the highest amounts are present in Brazil nuts [201] and in certain species of edible mushrooms (*Boletus edulis*) [202]. In a few clinical studies, prostate cancer patients were found to have lower levels of selenium in blood and toenails than controls [203]. The most striking reduction in prostate cancer incidence was discovered through a secondary analysis of data from a non-melanoma skin cancer study. The subjects were living in low selenium regions, and half of them were given brewer's yeast supplement containing 200 μg selenium per day for ten years. The inverse association with selenium supplementation was very strong (RR = 0.35, 95% CI 0.18 – 0.65), and prostate cancer risk was reduced for local and advanced tumors [204, 205]. The possible anticancer activity of selenium may be due to its presence in glutathione peroxidase, an antioxidant enzyme, which converts lipid peroxides to their corresponding alcohols, and hydrogen peroxide to water. Prostate secretory epithelium and prostate adenocarcinoma contain very little of this enzyme or selenium, compared to stromal cells, which do not develop neoplasia. Conversely, prostate epithelial cells are very rich in zinc, which resides mainly in their mitochondria. Prostate tissue contains ten-fold more zinc than other soft tissues, but two studies indicated decreased levels in prostate cancer cases [206, 207]. However, epidemiological studies are very inconsistent and do not support a protective effect of dietary zinc on prostate cancer incidence and mortality [203]. A case-control study, conducted in Greece [119], found a significant positive association of dietary zinc and risk of BPH (OR = 1.89, 95% CI 1.03 – 3.46, $p = 0.04$).

8 Genetic polymorphism and diet interactions

Recent studies of genetic variability indicate that polymorphisms of manganese superoxide dismutase, the primary antioxidant enzyme in mitochondria, may have a role in susceptibility to prostate cancer. Among Finnish smokers, men homozygous for the alanine (A) allele (AA) had a 70% increase in total prostate cancer risk and 3-fold risk of high grade neoplasia, compared with those possessing the valine (V) allele (VV or VA) [208]. Interestingly, AA frequency is more common in white Western population (50%) [209], than in the Japanese population (12%) [210], which may partly explain the difference in prostate cancer occurrence. However, possession of the AA genotype does not doom the men to prostate cancer, because the same genotype is particularly responsive to an antioxidant-rich diet [211]. In the US Physicians' Health Study, men with the AA genotype and a high intake of dietary antioxidants, confirmed by plasma levels of selenium, lycopene and α-tocopherol, had a greatly decreased risk of developing prostate cancer (RR = 0.60, 95% CI 0.39 – 0.88), especially in its aggressive form (RR = 0.40, 95% CI 0.25 – 0.69). Additionally, β-carotene treatment (50 mg every other day) proved protective against fatal prostate cancer among men with the AA genotype, but not among those with the other two variants (VV or VA).

Several studies have examined genetic variability of the heterocyclic amine activator enzymes, NAT and SULT, with regard to prostate cancer risk [130, 212]. Associations of the acetyltransferase genotype with prostate cancer risk were found [213], though a high rate of polymorphism complicated this assessment, because there are as many as 26 variant NAT1 and 26 variant NAT2 alleles [212]. In Portugal, homozygotes for NAT2*6 (slow acetylator genotype) were significantly more common among controls than among prostate cancer cases, but both constituted only a small proportion of this Southern European population (10.3 and 3.4%, respectively) [214]. A recent case-control study found that both the SULT genotype and phenotype (enzyme activity) were associated with higher risk of prostate cancer in African-American and white men [111]. The SULT1A1*1 high activity allele was more prevalent in

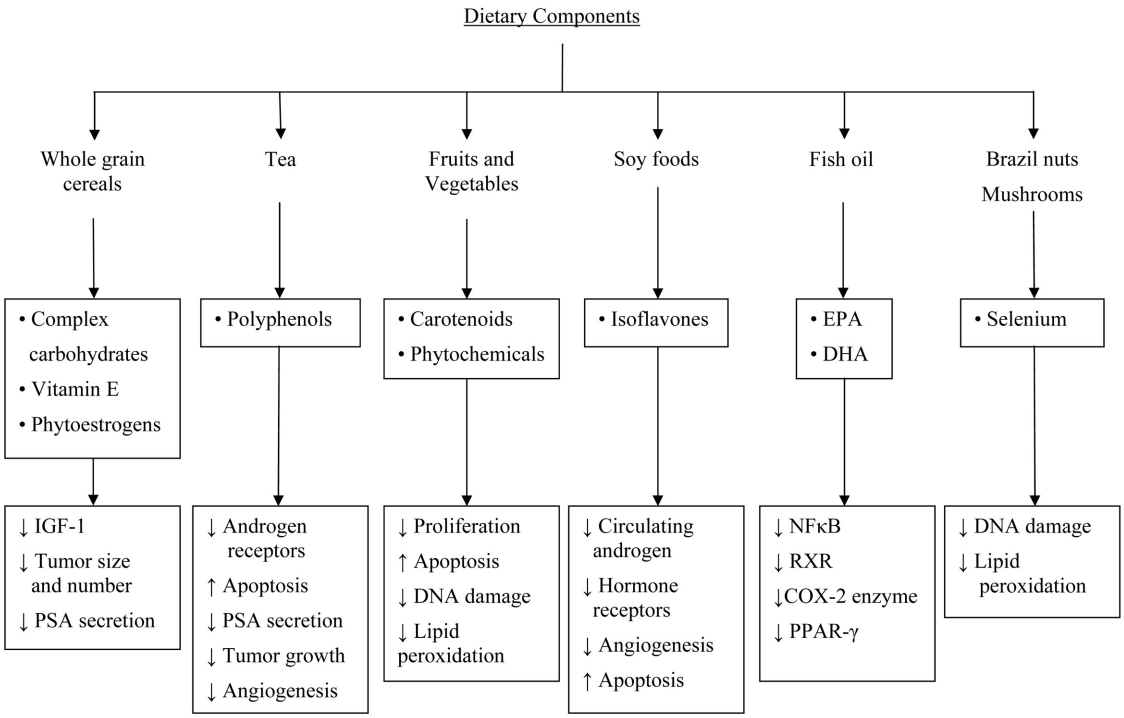

Figure 1. Dietary components associated with anti-carcinogenic activity in prostate.

African Americans (49.5% *vs* 35.2%), and it was more common in cases compared with controls (46.2% *vs* 38.5%).The risk significantly increased with higher activity of SULT1A1 in every tertile of well-done meat intake (sum of burgers, steaks, pork chops, bacon and sausage consumption). These and future studies of the association of dietary components with prostate cancer or BPH risk in genetically characterized subpopulations will help clarify diet recommendations for prostate health.

9 Whole diet effects

The human prostate is burdened by chronic diseases (BHP and cancer) associated with advancing age and, quite possibly, with an energy-rich oxidative environment provided by diets typically consumed in Western societies. As with other chronic diseases, there is the proverbial problem of proof, because a causal connection with relative nutritional deficiency or toxicity is difficult to establish [215], due to the long latency period of prostate disorders, multiple effects of nutrients or food-based bioactive compounds, and genetic polymorphism of study populations. Randomized trial outcomes cannot be as clear-cut as with pharmacological agents, since all subjects are usually exposed to the investigated nutrients, many of which have nonlinear threshold effects. Besides, we do not consume individual

Table 1. Provisional dietary recommendations for the maintenance of prostate health

Positive effects (recommended foods)	Negative effects (not recommended)
Energy restriction to maintain ideal weight	Excess energy intake resulting in obesity
Low-fat diet	High-fat diet
Marine fish oils	Animal fat, saturated fat
N-3 fatty acids	N-6 fatty acids
Phytanic and pristanic acid	
Fish	High meat intake (red meat)
	Processed and overcooked meat
Vitamin D (diet and sunlight exposure)	High intake of dairy foods
	>2 g calcium/day
Cereals (whole grains, rye bran)	Added sugars
Soy products	
Fruits and vegetables	
Antioxidant-rich colorful fruits and vegetables (carotenoids, anthocyanins)	
Tomatoes and tomato products	
Onions and garlic	
Cruciferous vegetables	
Hot chili peppers and turmeric	
Berries and pomegranate juice	
Wine, grape seed and hops extracts	
Brazil nuts and mushrooms	
Tea (green and black)	

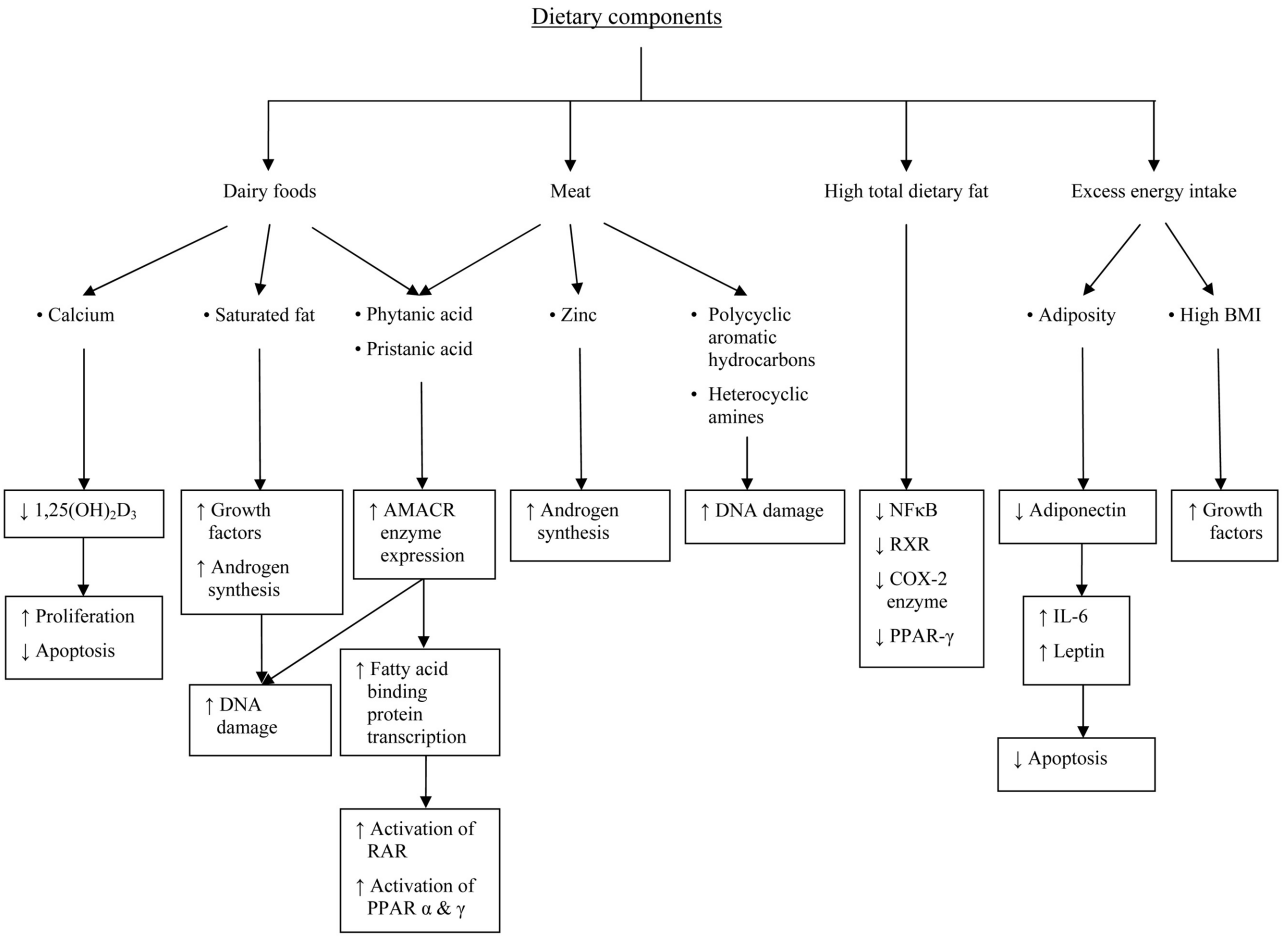

Figure 2. Dietary components associated with pro-carcinogenic activity in prostate.

nutrients but complex foods, whose effects on chronic diseases are even more difficult to evaluate. Epidemiological studies may indicate certain associations with the consumption of particular foods and are especially helpful when the investigated populations are greatly divergent in their dietary habits and in prevalence of particular chronic disease. The low incidence of prostate cancer in Southeast Asia and Japan, increasing prevalence among the immigrants from those regions to Europe and North America, together with the recent rise of both incidence and mortality associated with a rapid transition from traditional diets to Western fast food in many Asian urban centers [216], provide the strongest argument for the importance of nutritional factors in the development of prostate cancer. There are even indications that intensive lifestyle changes after diagnosis may affect prostate cancer progression. For example, among men with localized prostate cancer, high consumption of tomato sauce and fish decreased the risk of disease progression [216]. Prostate cancer patients, who refused any conventional treatment with surgery, radiation or androgen deprivation therapy, had a small but significant decrease in PSA among those assigned to a vegan diet of fruits, vegetables, whole grains, soy, supplemented with vitamins and minerals, while the control group experienced an increase in PSA and progrssion confirmed by magnetic resonance imaging [217]. A 70% growth inhibition was observed in LNCaP cells, exposed *in vitro* to serum of vegan diet patients, but a mere 9% for the control group. Therefore, healthy dietary choices and weight control are strongly recommended for the prevention and management of prostate diseases, with concurrent benefits for prevention of other forms of cancer, coronary heart disease and diabetes [218].

10 Conclusions and dietary implications

Figures 1 and 2 briefly summarize the positive and negative effects of various dietary constituents on prostate health. Figure 1 shows mostly foods of plant origin, predominantly identified through population studies and containing phytochemicals, associated with various physiological effects which may prevent prostate cancer or slow its progression. Various phytochemicals likely act in synergy in the context of a whole diet, therefore the increased intake of a single

food, or a single phytochemical, may be ineffective or even harmful in excess. Figure 2 includes foods mostly of animal origin, which are associated with a higher risk for prostate cancer and may contain bioactive compounds or promote a tissue environment favorable to prostate carcinogenesis. All of them are typical for Western diets and their intake increases with economic affluence. Table 1 provides simple recommendations for healthful dietary patterns, which include high intake of fruits and vegetables, tea, whole grain cereals, legumes and soy products, frequent consumption of fish and n-3 fatty acids, low intake of red meat and dairy products, avoidance of fried and grilled meat, and elimination of habitual overeating. The suggestions, derived from the most recent literature, differ little from diet recommendations for general health promotion from various advisory groups in every country. These patterns would ideally be followed through the whole life cycle, starting from childhood, to be most effective.

The authors have declared no conflict of interest.

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