Annu. Rev. Nutr. 1998. 18:413–40

DIET, NUTRITION, AND PROSTATE CANCER

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KEY WORDS: hormones, energy, fatty acids, vitamin A, vitamin D, carotenoids

ABSTRACT

Cancer of the prostate gland is one of the most common malignancies in affluent nations, in part due to the application of new screening and diagnostic tools. The development of life-threatening prostate cancer is the culmination of a complex series of initiation and promotional events over a period of decades and under the influence of many interacting genetic and environmental factors. A rapidly accumulating scientific literature provides compelling evidence for the hypothesis that diet and nutrition are important factors modifying risk of prostate cancer. Additional resources devoted to interactive research efforts by laboratory scientists and epidemiologists will provide further enlightenment and continued refinement of our assessment of risks and benefits for specific nutrients and dietary patterns. These studies provide hope that evidence-based dietary interventions will significantly impact the risk of prostate cancer and enhance the efficacy of therapeutic interventions.

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0199-9885/98/0715-0413$08.00

INTRODUCTION

The etiology of prostate cancer is poorly understood. Currently, however, knowledge concerning a diverse array of interacting genetic and environmental factors that contribute to risk is undergoing rapid growth. The role in the prostate cancer cascade of specific foods, dietary patterns, and nutrients has not been studied as vigorously as have many other diet and cancer relationships. Several fundamental observations suggest that the risk of developing prostate cancer is profoundly influenced by such environmental exposures. The wide range in age-adjusted mortality rates for prostate cancer observed among various countries (124, 192) cannot be attributed primarily to genetics. Within ethnic groups that migrate from low- to high-risk areas, mortality from prostate cancer increases significantly (65, 172). Furthermore, a temporal increase in prostate cancer incidence and mortality has occurred in several populations, for example among Japanese men in the decades following World War II (71) and among African-American males between 1930 and 1971 (37). Improvements in diagnostic technologies may have contributed to these trends, but they are unlikely to account entirely for the rising number of cases and deaths during the years prior to the development of prostate-specific antigen screening or modern imaging and biopsy techniques. It is estimated that among American men, during 1997, prostate cancer will account for 40% of all new cancer cases diagnosed (excluding skin cancer) and cause over 40,000 deaths (124). Prostate cancer currently ranks second, following lung cancer, as the underlying cause of cancer death, accounting for approximately 13% of all cancer mortality and 2.5–3.0% of all deaths among males. Furthermore, many men suffer impotence or incontinence of urine following primary therapy for prostate cancer, whereas others experience years of symptoms related to the slow progression

of metastatic disease. Prostate cancer has therefore emerged as a major concern for many Americans, and the costs to our health care system for screening, diagnosis, and treatment are growing rapidly. Opportunities for prevention must be identified, cost-effective preventive strategies tested, and programs established for the dissemination of knowledge to the medical community and the public. This chapter focuses on evidence that diet and nutrition play a role in the etiology and prevention of prostate cancer. Because it is critical that dietary hypotheses are integrated within a larger network of data concerning other etiologic factors, such as age and hormones, these are also reviewed briefly.

HISTOPATHOLOGY AND CLINICAL PROGRESSION

The prostate is one of several accessory sex glands of the male reproductive tract. It is located at the base of the bladder and in a healthy adult male weighs approximately 50 g. Interestingly, despite a similar embryonic origin, prostate cancer is common whereas cancers in the other accessory sex glands are rare. Furthermore, among hundreds of species examined, only humans and dogs have a significant risk for prostate neoplasia. The main function of the prostate is poorly understood, but it appears to be related to the production of secretions that aid in sperm function and in liquefying cervical mucous. The growth and development of the male prostate is largely controlled by sex hormones. The secretion of testosterone from the embryonic testis at approximately week 12 of fetal development stimulates prostate morphogenesis. It is possible, although speculative, that diet and nutritional factors modulating the fetal-maternal unit may alter the developing prostate and influence risk of cancer decades later. The prostate remains small until adolescence, when under the stimulation of male hormones during puberty it may rapidly grow from 5 to over 25 g. Subsequent increase in prostate size is more gradual and often associated with benign prostatic hyperplasia, a histopathologic process affecting the majority of men in affluent nations, and contributing to symptoms of prostatism in later decades of life (12, 32).

Prostate cancer exhibits a long preclinical phase or latency. This implies that diet and nutrition may influence prostate cancer progression at many stages of the male life cycle. Investigators are beginning to identify and characterize precursor lesions of prostate cancer. The continuum from normal prostatic epithelium, through preneoplasia or dysplasia, and culminating in prostate carcinoma is characterized by a number of features: progressive loss of markers of secretory differentiation, basal cell layer disruption, increasing nuclear and nucleolar abnormalities, greater proliferation, increased microvessel density, and progressive genetic instability (17). Prostatic intraepithelial neoplasia (PIN) is a putative precancerous stage and can be divided into two grades, low and high

(PIN 1 and PIN 2, respectively) (16). The incidence of PIN increases with age, and it is noted in a significant proportion of men by the third and fourth decades of life (63, 143, 154, 156, 157).

Latent prostate cancer is a poorly characterized term used to describe a lesion that is malignant by histopathologic criteria but found on postmortem examination of the prostate (62, 63). The terms microfocal and subclinical prostate cancer are also referred to in this context. The term latent is often interpreted as meaning low virulence, but the aggressiveness or the biological potential to become clinically relevant over time (if the person had survived) cannot be precisely ascertained by current histopathologic techniques. Autopsy studies from different geographic areas around the world suggest that latent prostate cancer can be detected in subjects after the third decade of life and is increasingly more common with age (63, 155, 157). Latent prostate cancer may be observed in 20–30% of men in their 50s and from 50–70% of men in their 80s (156, 185). Most of these lesions are small, typically unifocal, and primarily categorized as well to moderately differentiated (63). It is not known whether the origins and natural history of these lesions are distinct from tumors that become clinically significant or whether the latent cancers represent a continuum on a linear progression toward aggressive disease. If, indeed, these focal lesions represent a step in the pathway toward lethal prostate cancer, then the critical objective of our research is to identify and control the factors that accelerate progression from "latent" to clinical disease.

Prostate cancer shows heterogeneity in presentation and unpredictable rates of progression. Adenocarcinoma of the prostate typically spreads by local invasion through the capsule into adjacent organs, as well as via lymphatics and the vasculature to other tissues or organs. Metastases to the bone are common and a source of significant morbidity. The 5-year survival rates for prostate cancer are closely related to the stage at which the disease is initially diagnosed and treated. For men diagnosed with disease confined to the prostate, a 5-year survival rate of over 90% is expected, although many at that time have recurrent disease. For men initially presenting with distant metastases, fewer than 30% are expected to live 5 years with current therapy.

ENVIRONMENTAL AND GENETIC RISK FACTORS

Age

Prostate cancer is rarely detected prior to the age of 40, and the incidence rates increase rapidly for each subsequent decade of life. Although prostate cancer is typically considered a disease of older men, the high overall frequency in western nations makes prostate cancer a common malignancy in men between the ages of 50 and 70.

Genetics and Family History

A hereditary component of prostate cancer has been demonstrated, although the role of specific gene products remains poorly understood (60, 63). For example, men who have a first-degree relative with prostate cancer have a two- to threefold greater likelihood of developing prostate cancer compared with men without a first-degree relative with prostate cancer. However, the vast majority of prostate cancer cases, perhaps 90%, cannot be explained by rare and highly penetrant hereditary factors. We are beginning to appreciate the presence of genes exhibiting common polymorphisms that may modulate physiologic processes related to prostate cancer, such as androgen sensitivity (56, 85). It is probable that many yet-to-be-identified genetic polymorphisms modulating hormone secretion and action—as well as nutrient absorption, distribution, and metabolism—may contribute to risk.

International Variation, Migration, and Race

There is an approximately 30-fold difference between nations with the lowest rates of prostate cancer mortality, such as China and Japan, and those with the highest, such as the economically developed nations of North America, western and northern Europe, and Australia (124–126). In contrast, the age-specific prevalence of latent prostate cancer appears to exhibit less geographic and racial variation than does clinical or lethal prostate cancer, although the observed trends are parallel with those of clinical disease and mortality (2, 63, 185). Interestingly, the frequency of latent prostate cancer detected at autopsy in Japan increased from 22% in 1965–1979 to 35% in 1982–1986, in parallel with the continued Westernization of the Japanese diet (166).

Many studies of migrant populations moving from areas of low risk show an upward shift in incidence and mortality after living in nations exhibiting higher prevailing rates (65, 172). First-generation Asian-Americans experience rates that are approximately one third to one half those of Caucasian-Americans (65, 187). However, Japanese- and Chinese-Americans have a significantly, approximately three- to fivefold, greater risk than do native Japanese and Chinese (65, 187). Differences in detection strategies do exist between nations, but results of most migrant studies suggest a real shift in incidence toward rates of the host country, which supports the hypothesis that the international and racial differences in prostate cancer risk are defined primarily by environment and are not of genetic origin.

African-Americans experience one of the highest risks of prostate cancer in the world (116, 141). Stratification for socioeconomic and educational experience does not account for the greater incidence, presentation at more advanced stage, and overall worse prognosis than for their white counterparts (63, 116, 133, 135). The underlying causes of these racial differences remain

unknown. The low rates of prostate cancer in many black populations in Africa and the increase in risk in migrants moving to affluent nations suggest environmental factors are of primary concern (116, 141). The interacting roles of hormonal, dietary, genetic, and socioeconomic factors require additional examination (110, 116, 141).

Time Trends

It is believed that prostate cancer incidence and mortality rates have gradually increased worldwide over several decades (192, 193). The most rapid increase in mortality appears to be in those countries exhibiting the lowest base-line prostate cancer mortality rates. For example, the age-adjusted mortality from prostate cancer has increased almost eightfold in Japan over the 30-year period between World War II and 1980. In parallel, the rate in Hong Kong tripled over a 20-year period (1960–1980). During the same period, prostate cancer–specific mortality in the United States changed by only 6%. Some investigators have argued that much of the increase in prostate cancer incidence may be artifactual and due to more aggressive diagnosis and screening of the aging populations observed in many nations. Furthermore, the increased use of transurethral resection of the prostate (TURP) for treatment of benign prostatic hypertrophy has often detected unsuspected prostate cancer (117, 139). Many of the cancers detected by TURP seem to have low risk of progression and represent the latent forms observed at autopsy.

Demographic Risk Factors

Studies have not consistently identified a connection between socioeconomic status or educational level and prostate cancer risk (63). Interestingly, the excess risk in blacks persists across all socioeconomic strata (151). However, economic factors may influence availability and access to health care, as well as attitudes and concerns over health care and screening exhibited by various economic and ethnic subgroups, which could influence detection rates, stage of presentation, and mortality (142). Minimal differences between urban and rural residence have been observed. Specific religious groups have been examined relative to mortality rates of prostate cancer. In Utah, Mormons experience a 10–15% greater prostate cancer mortality than do other men in the same geographic region (105). Seventh Day Adventists, who like Mormons do not use alcohol, tobacco, or caffeine products but who advocate eating lacto-ovo vegetarian diets, experience a slightly lower incidence of prostate cancer mortality compared with the national norm (130, 131).

Occupational Exposures

Specific occupational-related exposures have been proposed as contributing factors to prostate cancer. However, based on present knowledge it is unlikely

that occupation accounts for an appreciable proportion of the prostate cancer cases. Workers in heavy industry, newspaper printing, farming, and rubber manufacturing, as well as those exposed to cadmium in the workplace, have been studied extensively without definitive conclusions (13, 15, 63, 179).

Tobacco

An association between prostate cancer incidence and tobacco use has been inconsistent, and most literature indicates that tobacco is not likely to be a major determinant of overall risk (107, 118). Nonetheless, a series of studies have reported higher incidence or mortality rates from prostate cancer among smokers (34, 35, 74, 75, 81). These observations are supported by preliminary data from the Health Professionals Follow-up Study, where smoking in the years just prior to diagnosis was related to more aggressive and lethal prostate cancer. The effects of smoking on prostate cancer risk could be mediated by carcinogens found in tobacco smoke or indirectly via alterations in the host internal environment, such as changes in hormone status or nutrient metabolism. Additional studies focusing on the critical timing of smoking during the life cycle and the specific stages of prostate cancer progression are necessary.

Sexual and Reproductive Factors

Some studies indicate an increased risk of prostate cancer with a higher frequency of intercourse and greater number of sexual partners (63). Furthermore, a higher prevalence of past venereal disease among case subjects than among control subjects is frequently observed. Because these patterns are similar to those observed for cancer of the cervix, it has been hypothesized that prostate cancer may also be related to infectious agents spread through sexual contact. Several epidemiologic studies have suggested a modest association between vasectomy and higher risk of prostate cancer, although other studies have not supported this link, and mechanisms remain to be identified (53, 63).

Endocrine Factors

Eunuchs and males with congenital abnormalities of androgen metabolism do not develop prostate cancer (63). The classic studies of Huggins and collaborators (77, 78) showed the profound sensitivity of prostate cancer growth and progression to androgens and led to the development of many strategies of androgen ablation for prostate cancer treatment. It has long been postulated that levels of endogenous hormone production may be related to risk of prostate cancer. Testosterone, which is converted by the enzyme 5-alpha-reductase to the active metabolite dihydrotestosterone (DHT), is the major hormonal regulator of prostate growth and function. Furthermore, sex hormone binding globulin (SHBG) binds circulating testosterone, thereby influencing the bioavailability of androgens, and may be a key modulator of hormone action. However, many

other hormones, such as prolactin, growth hormone, insulin-like growth factors, corticosteroids, estrogens, and thyroid hormone, participate in prostate biology.

Dozens of case-control studies have compared circulating testosterone levels and other hormones measured by immunoassays or biological assays (1, 52, 63, 118). Overall, results have been inconsistent, in part because of the limited power of studies involving small sample populations and relatively high within person variability. Often studies do not attempt to control for factors related to circulating hormone concentrations such as weight, age, smoking, alcohol, diet, and medications (43). Furthermore, case-control studies may be compromised by the effects of active prostate cancer or its treatment on hormone profiles. Prospective serological studies may overcome some of the methodological problems of case-control studies, but few have been completed. One such prospective study recently reported a strong trend of increasing prostate cancer risk with greater concentrations of plasma testosterone after adjusting for SHBG (46). In addition, higher levels of SHBG were related to lower prostate cancer risk.

A hormonal etiology may be the key factor associated with the higher risk of prostate cancer in African-American males (150). It has been proposed that African-Americans have higher testosterone levels than Caucasian males have. Indeed, some studies suggest a slightly greater level of nonprotein bound or free testosterone (not bound to SHBG) (40, 149). Furthermore, African-American women have higher concentrations of testosterone and estradiol during pregnancy than Caucasians have, and it has been hypothesized that these hormonal patterns acting in utero may influence the prostate cancer cascade in male children (68).

There have been few studies comparing prostate hormone receptor activity and risk of cancer. For example, the androgen receptor is a member of the steroid hormone receptor family and binds DHT. It is thought that environmental factors influence the physiological expression of the androgen receptor. Perhaps genetic polymorphisms in androgen receptor expression and function may also influence, along with serum concentrations of ligand, the risk of progression. The androgen receptor gene is highly polymorphic in humans. Genetic variations, such as the number of CAG repeats, may be correlated with transactivation activity and contribute to ethnic variations in prostate cancer risk (29, 56). We recently reported that hormone receptor density of the prostate can be modulated by dietary variables even when no changes in serum hormone profiles are detectable (27). Overall, it is clear that hormone profiles and receptor activity contribute to prostate cancer progression. However, more work is necessary in order to understand how environmental factors as well as genetic

polymorphisms controlling hormone synthesis, metabolism, and bioactivity may ultimately interact with diet and nutrition to modulate risk.

DIET AND NUTRITIONAL RISK FACTORS

Energy Balance: Caloric Intake, Anthropometrics, and Physical Activity

Energy intake is generally inadequately measured by the dietary assessment tools employed in large epidemiologic studies, and new techniques are needed (188). Cohort or case-control studies have, thus far, provided inconsistent results concerning the association between estimated energy intake and prostate cancer risk (51, 54, 145, 163, 183, 186). One study reported that men whose intake of energy is in the upper-most quartile experienced a strongly elevated risk for prostate tumors that exhibit more-aggressive behavior (183). Increased energy intake, particularly from saturated fat, was associated with greater risk in African-Americans, Caucasian-Americans, and Asian-Americans (186). Laboratory studies have demonstrated that modest diet or energy restrictions reduce the incidence or growth of many experimental cancers in rodents. We recently investigated the hypothesis that dietary energy intake may modulate experimental prostate carcinogenesis. Preliminary studies using the Dunning R3327H well-differentiated, slow-growing, transplantable prostate adenocarcinoma show that energy restriction produces a dose-dependent inhibition of prostate tumor growth. Furthermore, the source of energy restriction appears to be less important than the degree of energy restriction. A similar inhibition in tumor growth is observed when diets are restricted in fat calories or carbohydrate calories.

Although in large studies accurate height and body weight can be obtained, quantifying abdominal versus peripheral obesity, body composition, and other anthropometric measures is problematic. Nutritional factors that influence body anthropometrics early in life may also affect future prostate cancer risk, but these measurements are also difficult to assess retrospectively. For example, one study has suggested an association between increased incidence of prostate cancer and high birth weight, which in turn suggests that the prenatal maternal environment interacting with genetics has a lifelong effect on the prostate (178). Taller individuals appear to be at higher risk for several malignancies (4, 5), and some, but not all, studies suggest a similar association for prostate cancer (7, 55, 59, 67, 91, 190). Attained height is critically dependent on childhood and adolescent nutrition. This developmental period is characterized by profound changes in levels of sex hormones, growth hormone, and insulin-like growth factor-1, as well as by the development of the prostate gland. Energy intake is

but one of many nutritional variables modulating these processes during adolescence and is not easily documented by diet-assessment tools employed decades later.

Studies of prostate cancer have yielded inconsistent results concerning the relationship between various measurements of adult body mass or obesity and risk (55, 91, 93, 96, 103, 152, 169, 175, 176, 183, 186). In males, obesity is associated with higher serum estrogen and lower testosterone levels (6, 10, 43, 127), a hormonal pattern that would be predicted to decrease risk of prostate cancer. Indeed, preadult (age 10) obesity was related to a lower risk of advanced or metastatic prostate cancer later in life (55). Body mass index (BMI) has often been employed as a measure of obesity, but the BMI is correlated with both adiposity and lean body mass and may not prove to be the best surrogate marker for assessing alterations in energy balance and prostate cancer risk (49). The results from one prospective study indicated that an observed positive association between BMI and prostate cancer risk was due to lean body mass (assessed by upper-arm circumference) rather than to the level of adiposity (162). These results suggest that BMI may be a confounded measure of obesity and that future studies should include additional assessments of obesity and lean body mass in order to dissect their independent contributions to risk.

Data regarding physical activity and prostate cancer are relatively sparse (3, 20, 122, 134, 163, 180, 191). A modest inverse relationship between physical activity and risk of prostate cancer had been suggested in several studies (3, 20, 100, 101, 177, 180). However, others have found no association (163, 191), and two studies indicated an increased risk of prostate cancer among men who were more physically active during young adulthood (122, 134). One large cohort study of Harvard alumni found a lower risk for men who expended an extraordinary amount of energy (101). A study from China reported a slight excess of prostate cancer among men whose occupations entailed low activity levels, but the study was seriously limited by the inability to control for potential confounders (76). Overall, it is not clear how physical activity may independently or by interaction with the diet alter prostate cancer risk. Furthermore, potential mechanisms of action and periods of life during which the physical activity may be most relevant remain to be explored.

The effects of energy balance and anthropometrics on hormone status is of critical importance for the understanding of prostate cancer risk. Physical activity is associated with lower testosterone levels (64, 173). Among the many hormones that may be altered by changes in energy intake is insulin-like growth factor-1 (IGF-1) (27, 39, 79). IGF-1 levels are reduced by lowering energy and protein intake (82). Prostate epithelial cells have IGF-1 receptors, and IGF-1 stimulates proliferation in the presence of DHT in androgen-dependent prostate cancer cell lines (30, 31, 102). Moreover, circulating IGF-1 correlates with

growth rates in adolescence and childhood and with adult lean body mass. Recent findings from a cohort study suggest that circulating IGF-I concentrations adjusted for its binding protein in prospectively collected samples are positively related to future risk of prostate cancer (21a). Furthermore, in mice bearing the LNCaP prostate tumor, energy restriction is associated with reduced tumor growth and lower concentrations of IGF-I. These studies suggest that IGF-I may be a key biomarker and potential mediator of changes in energy balance and in risk of prostate cancer.

Dietary Fat and Fatty Acid Profiles

National per capita total fat consumption among nations of the world is strongly correlated with mortality rate from prostate cancer (8, 21, 26, 189a). Although the evidence from case-control studies and prospective cohort studies is not entirely consistent, the results generally show a positive relationship (58, 69, 89, 93, 115, 119, 152, 153, 159, 175, 183). For example, the Health Professionals Follow-up Study (54) of 51,521 men in the United States found a weak though nonsignificant trend for total fat intake (RR $=$ 1.7) after adjusting for total energy intake. A comprehensive case-control study among African-Americans, Caucasian-Americans, and Asian-Americans also observed a slight increase in risk with greater total fat intake across all ethnic groups (186). Case-control and cohort studies have not provided consistent results regarding the specific dietary fatty acid patterns and their major food sources and prostate cancer risk (189). In general, evidence supports a positive relationship between prostate cancer and saturated fat or animal fat (54, 58, 69, 80, 99, 114, 146, 183, 186, 189a). Few investigations have focused on the role of monounsaturated lipids, and the results are inconsistent (54, 80, 183, 186, 189a). A slight, nonsignificant increase in risk of advanced prostate cancer was observed for monounsaturated fats in the Health Professionals Follow-up study (54). The evidence concerning diets rich in polyunsaturated fats is also inconclusive (80, 146, 189a). A strong association was observed between the estimated intake of α-linolenic acid, with a relative risk of 3.4 for men in the highest quintile of intake (54). Efforts to utilize blood fatty acid profiles as a surrogate marker of intake and to define the relationship to prostate cancer risk are underway. The association between plasma phospholipid fatty acid profiles and the development of prostate cancer was examined in a nested case-control design (47). The only significant relationship observed was between increasing concentrations of plasma α-linolenic acid and greater prostate cancer risk. In vitro studies have shown that linoleic acid stimulates the growth of prostate cancer cells in culture (148). Although omega-3 fatty acids appear to inhibit the growth of prostate cells in culture, the epidemiologic studies have not shown a significant relationship with risk (54, 80, 189a).

The effects of dietary fat concentrations on prostate tumorigenesis have been examined in a few rodent models (28, 136, 147, 148, 181). Essential fatty acids are required for the growth of the well-differentiated hormone-dependent Dunning adenocarcinoma, although in the same studies a large range of intake (12–40% of total energy intake) of dietary fat derived from corn oil had no effect on tumor growth rates (28). In contrast, a range of 20–40% of total energy intake from fat increased the growth of the poorly differentiated LNCaP human prostate adenocarcinoma transplanted into mice (181). Two studies have reported that mice fed diets rich in omega-3 fatty acids experienced slower growth of human prostate tumor cell line xenografts (88, 147). No major effects of dietary fat concentration on two carcinogen-induced prostate tumor models were noted (140, 165). Additional studies comparing whole-grain diets with diets supplemented with fat added by dilution to the control diet suggested an increase in tumor incidence in the high-fat–fed group (136, 137). Another study showed that rats fed high-fat diets developed more atypical hyperplasia and spontaneous cancers, but energy intake was also much higher in those fed the high-fat diets (94). The possibility that diets varying in fat content or having specific fatty acid patterns may modify the progression of prostate cancer is a viable hypothesis that requires additional investigation. Some studies suggest that high-fat diets alter hormonal environments (70), whereas others do not support that idea (27, 28, 43).

Protein

Data are limited concerning the relationship of total protein or animal versus vegetable protein and the risk of prostate cancer. In several studies positive associations have been suggested between total protein intake and prostate cancer risk (8, 183). Two studies associated consumption of vegetable protein and lower risk (44, 114). Soy products, consumed in greater amounts in low-risk Asian populations, may have beneficial effects on prostate cancer (109). However, this hypothesis has not been adequately tested in human and laboratory studies. Diets restricted in total protein and energy are associated with reduced growth of rat prostate tumors in association with reduced concentrations of serum androgens, growth hormone, and prolactin, as well as reduced density of prolactin receptors in prostate tissue (27). It is premature to make any judgment about the independent role of dietary protein concentration or source on prostate cancer risk.

Alcohol

The relationship between alcohol consumption and risk of prostate cancer has been evaluated in a series of studies. No strong evidence has emerged for an association (152, 163, 191, 189a).

Poultry, Meat, Fish, and Dairy Products

Reports of a correlation between diets rich in meat or dairy products and risk of prostate cancer are frequent (8, 47, 54, 75, 99, 111, 114, 163, 169, 174, 175, 183). The majority of cohort and case-control investigations of populations whose overall meat intake is high detect an increased risk associated with greater consumption. Initial cohort studies yielded conflicting results, but in several of the null studies long intervals occurred between dietary assessment and diagnosis of cancer, or they were based on relatively crude dietary measurements (75, 163). Two cohort studies of Seventh-Day Adventists (114, 169) found that men who consumed relatively large amounts of animal products were at greater risk of incident and fatal prostate cancer. Three recent cohort studies found similar positive associations between prostate cancer and the consumption of red meat (47, 54, 99), of total animal fat (54), and of fatty animal foods (99). In these later studies, dietary intake was assessed relatively shortly before diagnosis, mostly within 5 years, suggesting that diet may influence later stages of prostate carcinogenesis. Several of the studies observed a stronger association between meat and indicators of disease progression, such as higher stage, presence of metastases, and mortality (54, 183). Comparisons of diets high in animal fats or red meat showed an increased relative risk for prostate cancer approximately twofold over diets low in these products. Relative risk measurements of this magnitude, however, should be viewed with caution. High intake of red meat may be correlated with some other poorly understood component of lifestyle or diet that mediates the observed relationship. Potential mechanisms whereby meat products can directly alter risk are speculative. Until more definitive data are generated, consumption of 3 oz of meat (red meat, fish, and poultry) per day as part of a healthy diet in accordance with the current American guidelines defined in the food pyramid remains a reasonable guideline.

The impact of egg consumption on risk of prostate cancer has been examined in a series of cohort and case-control studies (75, 99, 114, 146, 169, 174, 186). The data are inconclusive.

A relationship between dairy products as a source of saturated fat and risk of prostate cancer has been detected in some studies (8, 95, 99, 111, 146, 163, 169, 174) but not in others (75, 114). In an analysis based on diet history conducted in Hawaii, there was a high correlation ($r = 0.9$) between intake of animal fat and saturated fat from meat and dairy products and incidence of prostate cancer (92). In regions of Italy, positive correlations were found between prostate cancer mortality, economic indicators such as gross national product ($r = 0.72$), and several dietary items, including per capita milk intake ($r = 0.75$) and cheese consumption ($r = 0.69$) (36, 112). The associations observed between milk and cheese intake and prostate cancer incidence persisted in multivariate analyses. A recent case-control study found positive associations between

saturated fat and prostate cancer risk among African-Americans, Caucasian-Americans, Chinese-Americans, and Japanese-Americans (186). The associations were particularly strong for advanced cancers, and the source of animal fat most strongly and consistently associated with high risk in the case-control studies was dairy products.

As reviewed above, consumption of diets high in animal fats, meats, or dairy products increases the relative risk of prostate cancer approximately twofold compared with diets low in these foods. But relative risks of this magnitude are suggestive, not firm proof of a causal association. Furthermore, diets rich in meat and dairy products often are also high in total fat and saturated fat. It is difficult to disentangle these interrelated variables, and perhaps other lifestyle factors, and obtain a clear representation of the risk associated with any one of these food items. To date, none of the mechanisms proposed to explain the association between animal fats, meats, and dairy products and risk of prostate cancer are convincing. It is possible some combination of total energy, macronutrient, and micronutrient intake associated with this dietary pattern underlies this relationship.

Vitamin E

Few studies have evaluated the role of vitamin E in risk of prostate cancer. A case-control study from Canada showed no relationship (145). Two nested case-control studies examined serum tocopherol concentrations relative to risk, with inconsistent results (66, 73). Prediagnostic blood vitamin E levels in American men were associated with lower risk in younger (<70 years old) men but higher risk in older men (73). A study in The Netherlands reported a nonsignificant decrease (RR = 0.6) in risk for those with serum levels in the highest quintile (66). The most provocative data are derived from a randomized interventional trial conducted in Finland among men at high risk of lung cancer (5a). A statistically significant inverse association between vitamin E supplementation and risk of prostate cancer was observed (5a). Additional studies are necessary: to investigate these relationships with men of differing ages, to define optimal intake via the diet or as supplements, and to explore how vitamin E may modulate risk.

Vitamin A

An adequate intake of vitamin A or retinol is necessary for normal growth and physiologic function of the prostate. With the recent identification and characterization of the vitamin A binding proteins and the retinoid receptors, the importance of vitamin A in the control of cellular differentiation and proliferation is beginning to be understood at the molecular level. Beginning over 40 years ago, studies reported that vitamin A deficiency in rodents will

produce a squamous metaplasia in the prostate (11). Histologic changes such as these are often thought to predispose a tissue to malignant transformation. In organ culture studies of prostate tissue, retinol was shown to reverse squamous metaplasia induced by treatment with chemical carcinogens (11, 97). Retinol binding proteins have also been reported in prostate cells (18, 50, 83). We recently reported vitamin A concentrations in the prostate at 1–3 nmol/g, which is within a range where biological effects have been observed in vitro (25). A recent in vitro study (129) showed that primary cultures of prostatic epithelial cells grown under serum-free conditions exhibit a biphasic growth response to vitamin A. Retinoic acid provided at 3-nm concentrations or greater was found to inhibit proliferation, whereas lower concentrations were stimulatory. A similarly biphasic growth response has been observed in organ culture of rat prostatic tissue for 13-*cis*-retinoic acid–stimulated prostate cellular proliferation and branching of ducts at lower concentrations but was reversibly inhibitory at higher concentrations. Furthermore, the synthetic retinoid N(4-hydroxyphenyl)retinamide (4HPR) was not effective in this model. Others have observed that the retinoids appear to inhibit testosterone-induced hyperplasia in mouse prostate explants (23). Although it remains to be clearly defined, it has been hypothesized that retinoic acid may influence the conversion of testosterone to DHT via 5-α-reductase (84) or the proliferative response to growth factors (22). 4HPR exhibits cytotoxic effects on cultured prostate cancer cells (132) and inhibits carcinogen- and androgen-induced prostate cancer (138) and ras- and myc-associated prostate cancer in a reconstitution model (168) but not spontaneous (120) prostate cancer in rodent models.

That vitamin A is a key factor regulating the growth and differentiation of normal and malignant prostate cells is indicated clearly in laboratory studies. In contrast, however, epidemiologic data is frequently conflicting or contradictory (108, 189a). Higher intake of vitamin A has been associated with a slightly increased risk of prostate cancer in some studies and lower risk in others (57, 58, 69, 73, 90, 145, 174, 183). Several investigations observed a greater risk of prostate cancer with lower serum concentrations of retinol (66, 73, 144). It is important to recognize that serum retinol concentrations are not linearly associated with dietary intake. Indeed, serum concentrations are under tight homeostatic control within a rather narrow range except at the extremes of intake. A clear picture for the role of vitamin A in prostate cancer has yet to emerge. Based on the human epidemiologic data and the laboratory studies, it is reasonable to postulate that vitamin A and related metabolites or synthetic retinoids can modulate prostate function and perhaps influence various steps in the progression of prostate cancer. However, much more work is needed relative to the prostate in order to unravel the complexities of vitamin A nutrition in free-living populations and the myriad potential interactions with other dietary

factors, with genes controlling the steroid receptor superfamily, with genes controlling retinoid metabolism and degradation, and with the endocrine system.

Fruits, Vegetables, and Carotenoids

In contrast to the accumulated evidence for many other cancers affecting a diverse array of organs, overall consumption of fruits and vegetables has not shown a consistent reduction in risk of prostate cancer (14, 57, 75, 98, 114, 146, 159, 163, 164, 169, 174, 175, 189a). The role of β-carotene in prostate cancer has been the subject of several human studies but has not received attention in laboratory animal experiments. Estimated intake of β-carotene has been associated with increased risk (75, 98), decreased risk (75, 111, 119), or no effect (57, 75, 152) on human prostate cancer incidence or mortality. The positive association observed with β-carotene for prostate cancer risk in Hawaii was found to be entirely due to papaya intake (75, 98), not to other sources of β-carotene. The significance of this observation remains to be defined. Furthermore, a recent interventional trial showed no benefit from short-term β-carotene supplementation on risk of prostate cancer (5a). β-Carotene is one of several carotenoids that can be metabolized to form vitamin A in mammals. Furthermore, the absorption, distribution, and metabolism of β-carotene and its conversion to vitamin A either in the liver or in peripheral tissues remains poorly understood (41, 123). We recently observed that prostate cancer cells in culture can convert β-carotene to retinol (AW Williams, T W-M Boileau, JR Zhou, SK Clinton, JW Erdman Jr, preliminary data). Furthermore, we recently reported the presence of β-carotene in the human prostate at concentrations that exceed retinol (25). Overall, the data suggest that a complex relationship may exist between retinoids and the pro-vitamin A carotenoids in the prostate cancer cascade. It is unlikely that human studies focusing on estimated intake of β-carotene and prostate cancer risk can answer our hypotheses. The many genetic and dietary covariables modulating the absorption, distribution, and biological activity of β-carotene, as well as its conversion to vitamin A, need to be elucidated before a clear understanding can emerge.

Over 600 different carotenoids have been characterized in nature, and only a small proportion can contribute to the vitamin A requirement (121). Approximately a dozen carotenoids account for the majority of dietary intake and are found in detectable concentrations in human blood or tissues (25, 158, 171). For example, lycopene is a predominant carotenoid in plasma and tissues of affluent populations (9, 86, 87). Lycopene, which cannot be converted to vitamin A, is the most efficient quencher of singlet oxygen among the common carotenoids (38). As data for content of lycopene and other major carotenoids in foods became available in recent years (106), epidemiologists began to examine the relationship between several carotenoids and risk of prostate cancer. For example,

carotenoid intake was assessed in a cohort of male health professionals in the United States (57). Estimated intake of β-carotene, α-carotene, lutein, and β-cryptoxanthin was not associated with risk of prostate cancer. In contrast, men in the highest quintile of estimated lycopene intake experienced a 21% lower risk. Over 80% of dietary lycopene intake in the United States is derived from tomato products whereas pink grapefruit, watermelon, guava, apricot, and papaya provide the remainder (106). Consumption of tomato sauce was the strongest predictor of lower prostate cancer risk in the cohort. Men consuming two or more servings per week have a 36% reduction in risk compared with men who rarely or never consume tomato sauce. In addition, consumption of tomatoes and pizza was associated with lower risk.

Additional epidemiologic data examining the association between tomatoes or lycopene intake and risk of prostate cancer also suggest a benefit. Tomato intake was the specific dietary factor most strongly related to lower risk of prostate cancer in a cohort study of Seventh-Day Adventists (114), and one case-control study found a nonsignificant inverse association between tomato intake and risk of prostate cancer (159). The only published study that examined prediagnostic serum carotenoids and risk of prostate cancer found an inverse association with lycopene, but not other carotenoids (73). That study included only 103 cases, and these associations were not statistically significant (73). Lycopene has the highest mean concentration of any carotenoid in the human prostate (25). Interestingly, approximately 18 different isomers of lycopene are detected in prostate tissue and at least 12 are found in serum (25). *Cis* isomers of lycopene account for the majority of tissue and circulating lycopene (25). The biological significance of isomer patterns remains to be defined. Overall, investigators should use caution in assuming that lycopene mediates a relationship between consumption of tomato products and lower risk of prostate cancer. Much is still to be learned about mechanisms of lycopene absorption, deposition in the prostate, local metabolism, factors modulating tissue concentrations, and biological properties that may inhibit the prostate cancer cascade. Interestingly, the sucrose polyester (Olestra) developed by the food industry as a fat substitute has been shown to reduce plasma lycopene concentrations (184).

Selenium

Selenium intake has been examined relative to the risk of many cancers, though little emphasis has been directed toward prostate cancer (189a). A recent study was designed to examine the effects of selenium supplementation on recurrence of skin cancer in a high-risk population (24). Selenium treatment did not influence the risk of skin cancer, although selenium-treated patients had a nonsignificant reduction in all-cause mortality and a significant reduction in total cancer mortality, as well as a lower risk of prostate cancer (24). Additional

studies are necessary to confirm a relationship with prostate cancer and further define mechanisms of action.

Calcium, Phosphorus, and Vitamin D

Calcium, phosphorus, and vitamin D are interacting components of a complex network of nutritional and endocrine pathways designed to maintain optimal concentrations of these critical elements within a tightly regulated internal environment. Few studies have addressed the interface between these components and the risk of prostate cancer. Vitamin D has been hypothesized to protect against prostate cancer based on both epidemiologic and laboratory evidence. Being of an African race and residing in northern latitudes (lower sunlight exposure) are factors potentially associated with lower serum levels of vitamin D and are related to an increased risk of prostate cancer (161). However, direct evidence regarding vitamin D intake or serum concentrations and prostate cancer risk is limited. Two recent studies based on stored blood samples found that men who had high levels of $1,25(OH)_2$-vitamin D simultaneously with low levels of 25(OH)-vitamin D were at lowest risk of developing prostate cancer (33, 48). In particular, risk of anaplastic and palpable tumors was remarkably low in these studies when the concentration of $1,25(OH)_2$-vitamin D was high. However, another study based on a limited number of cases found no association (19).

A protective role of $1,25(OH)_2$-vitamin D, the physiologically active form of vitamin D, is also supported by evidence that prostate epithelial cells possess vitamin D receptors, and $1,25(OH)_2$-vitamin D induces differentiation while inhibiting proliferation of established prostate cancer cell lines and in cultures of human prostate epithelial cells established from tissues (42, 72, 113, 128, 167). Analogues of $1,25(OH)_2$-vitamin D have also been shown to possess a modest ability to alter the growth of implanted human prostate carcinoma cells in nude mice and in chemically induced, androgen-promoted prostate cancers in rats (104, 160).

Although the in vitro and animal data and the limited-but-promising human data are intriguing, no observational or intervention study has demonstrated that a higher intake of vitamin D from dietary or supplemental sources lowers risk of prostate cancer. On the contrary, consumption of dairy products, the major dietary source of vitamin D, frequently has been associated with a higher risk of prostate cancer in ecological, case-control, and cohort studies (see above). This seemingly paradoxical finding may be explained by the overall impact of diet on serum $1,25(OH)_2$-vitamin D levels. $1,25(OH)_2$-vitamin D is a highly regulated hormone responsive to fluctuations in serum calcium and phosphate and is not related to dietary vitamin D within normal ranges of dietary intake. Decreasing dietary calcium lowers plasma calcium levels, thereby stimulating the release of parathyroid hormone, which in turn increases the activity of 1-α-hydroxylase in the kidney to convert 25(OH)-vitamin D to $1,25(OH)_2$-vitamin D. Dairy

products are generally the major providers of dietary calcium. Thus, if high levels of 1,25$(OH)_2$-vitamin D are protective, high consumption of dairy products—by providing highly bioavailable calcium, which will tend to lower 1,25$(OH)_2$-vitamin D levels—may be deleterious.

Calcium intake is closely linked to vitamin D metabolism and inversely related to 1,25$(OH)_2$-vitamin D. Recent results from the Health Professionals Follow-up Study suggest that the consumption of calcium from dairy or nondairy sources, including supplements, is associated with an increased risk of aggressive prostate cancer (55a). These relationships have been confirmed in a Swedish case-control study. The relationship between calcium intake and prostate cancer was strongest among older men. Interestingly, aging is known to be associated with reduced calcium absorption, lower production of 25(OH)-vitamin D, a decline in serum 1,25$(OH)_2$-vitamin D concentrations, reduced absorption of intestinal vitamin D, decreased conversion by renal hydroxylase of 25(OH)-vitamin D to 1,25$(OH)_2$-vitamin D, and a reduction in vitamin D receptors (182). In these studies, no effect was noted between dietary phosphorus and risk of prostate cancer. Phosphorus was examined because hypophosphatemia activates 1-α-hydroxylase to convert 25(OH)-vitamin D to 1,25$(OH)_2$-vitamin D. Overall, the preliminary results of the Health Professionals study show that dietary vitamin D intake ranging from >150 to <800 IU/day showed no relationship to risk of prostate cancer. In contrast, higher consumption of calcium was associated with increased risk of aggressive or more advanced prostate cancer, with a threefold increase in risk for intakes >2 g/day compared with men consuming <500 mg/day. The relative risk was even greater when metastatic cancer or fatal cancer was considered. Calcium from both dairy and nondairy sources including dietary supplements independently increased risk. The surprising data suggesting a role of calcium intake in prostate cancer risk, particularly aggressive prostate cancer, are of enormous importance considering the recent increases in the recommended daily intake of calcium and the importance of calcium in maintaining health in aging individuals.

Overall, the evidence is accumulating that the calcium:phosphorus:vitamin D axis is a factor in prostate growth, differentiation, and risk of cancer. However, the mechanisms whereby these interacting components modulate risk, how they interface with many genetic polymorphisms involved in these pathways, and how we can develop dietary guidelines for these nutrients to maximize health and reduce risk of prostate cancer remain important questions.

SUMMARY

Current knowledge of prostate cancer risk does not provide definitive information for allowing confident recommendation of specific interventions for

prevention. However, the evidence is accumulating rapidly, and general guidelines and approaches will gradually emerge (6a, 189a). It is important for nutritional epidemiologists and laboratory scientists to integrate their concepts concerning diet into a broader understanding of the prostate cancer cascade. We recognize that prostate cancer is a slowly progressing disease that begins decades prior to diagnosis and may even be influenced by in utero exposures and factors active during puberty and adolescence. Data examining preadult dietary patterns and risk of prostate cancer are sparse. Premalignant lesions are observed in a significant portion of men in the third and fourth decades of life, years before prostate cancer is detected in the clinic. The high prevalence of "latent" prostate cancer compared with clinically significant disease suggests that dietary factors influencing the later stages of prostate cancer progression may be relevant to effective intervention. Indeed, many of the human studies suggest that diet is a key factor in the etiology of aggressive and lethal forms of prostate cancer, which further emphasizes the importance of investigating the role of diet in the biological processes involved in invasion and metastases. Interactions between diet, endocrine profiles, and prostate hormone receptor patterns and signal transduction remain poorly understood but are critical pathways for prostate cancer progression. The role of genetics in prostate cancer risk is just beginning to emerge and much is to be learned about how diet and nutrition may alter the penetrance of genes that modulate risk. Germ-line mutations and genetic polymorphisms that identify high-risk subgroups for early prostate cancer are beginning to be identified. The high-risk subgroups or other subgroups based on familial history of prostate cancer will allow us to select men for intervention studies that are highly motivated and will be compliant with specific dietary interventions. The success of intervention studies will be enhanced by the development and characterization of surrogate markers for nutrient intake and their biological effects. Although few rodent models for prostate cancer have been established, molecular techniques are allowing investigators to develop new murine systems with specific genetic lesions relevant to human disease. Animal models allow nutritional scientists to investigate, under precisely controlled conditions, many of the complex hypotheses generated by prospective and case-control human studies. Prostate cancer is a disease of multifactorial etiology and the key to understanding the progression and defining prevention programs will be found through multidisciplinary interactive research efforts involving epidemiologists, nutritional scientists, and cell or molecular biologists.

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