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Macronutrients, Micronutrients and Prostate Cancer

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Introduction

Prostate cancer is a major cause of mortality in North America. In the U.S., prostate cancer is the second leading cause of cancer death among males, and accounts for almost 30% of all cancers diagnosed. Our understanding of the causes of prostate cancer remains far from complete. The only established risk factors include older age, a family history of prostate cancer, and race, with risk greatest among African Americans, followed by Caucasians and Asians. Few modifiable risk factors are universally accepted as established. Nonetheless, several lines of evidence indicate that nutritional or other environmental factors profoundly influence the occurrence or progression of this cancer.

The first clue that nutritional or other lifestyle factors influence prostate carcinogenesis is that prostate cancer incidence rates display substantial variability across countries around the world. An almost 70-fold differential in age-standardized prostate cancer rates has been observed between the populations with the lowest and highest rates[1]. These differences are likely to result largely from nongenetic factors because the incidence of prostate cancer increases in populations that have migrated from countries where the rates are low to those where rates are high. Another indication that nutritional or related factors influence risk of prostate cancer is that high correlations are observed between per capita consumption of fat, animal fat, red meat and dairy products and national prostate cancer incidence and mortality rates[2].

This report will review the epidemiologic evidence for specific macronutrients and micronutrients that either enhance risk or may protect against prostate cancer. Before considering the role of specific nutrients, it is important to appreciate that sex steroids and the insulin-like growth factor (IGF) and vitamin D axes appear to influence the occurrence and progression of prostate cancer. Individual prostate cancer risk may be determined largely by normal variation in the blood levels of the hormones, or their binding proteins, and by genetic variation in their receptors. Because this variation is influenced both by external factors and by heredity, hormonally-related factors are likely to be at a critical interface between many of the nutritional and other environmental factors, and prostate cancer risk.

Macronutrients

The substantial variability of prostate cancer incidence and mortality rates around the world is believed by many to result from specific dietary and nutritional patterns[1]. Prostate cancer rates are lowest in Asia, and highest in Western Europe, Australia, and North America. These regions differ in dietary patterns, overall nutritional status and other lifestyle factors. National per capita consumption of various nutritional variables correlate strongly with national prostate cancer mortality rates, suggesting that nutritional factors influence the occurrence or progression of prostate cancer[2]. For example, a correlation with milk and dairy products has been among the most consistent associations observed with prostate cancer mortality. While the importance of nutrition is generally accepted, what the specific factors are remains unclear. Total fat, saturated fat, and animal fat are hypothesized to be the relevant factors, but these may be markers of other important dietary factors.

Total Energy Intake and Energy Balance

Energy balance is a critical factor for cancer, including prostate cancer, in numerous animal models. In rodent models of transplantable prostate tumors, in which energy-related parameters can be carefully controlled, a 20 to 30% lowering in energy intake reduced levels of insulin-like growth factor, a tumor promoter, and reduced tumor size[3]. Importantly, these changes did not differ whether the restriction was induced by lipid or carbohydrate restriction. Unlike animal models, for which energy intake can be closely controlled, the examination of total energy intake as a risk factor for prostate cancer in free-living populations is fraught with difficulties. Nonetheless, it is likely that overconsumption of calories enhances risk of prostate cancer, though it is unclear during which age period this effect is likely to be most important.

Animal and Saturated Fat

National per capita fat consumption correlates with national prostate cancer incidence and mortality rates[2]. Animal sources of fat, primarily from red meat and dairy sources appear most strongly related to risk. In general, most case-control (retrospective) and prospective epidemiologic studies tend to find that men who consume higher levels of animal fat are at higher risk of developing prostate cancer. It is unclear at present what is the critical component. Some suggest saturated fat is important, but this is not established. There may even be a non-lipid component of a diet high in animal fat that is the causative factor. Long chain omega-3 fatty acids, primarily from fish oils, have been hypothesized to lower risk of cancers, including prostate cancer, but human data have been quite sparse. The omega-3 fatty acids found in fish may be beneficial. Replacing red meat with more fish in the diet, likely to lower heart disease risk, may also have some benefit against prostate cancer.

Dairy Products and Calcium

National per capita milk consumption correlates highly with national prostate cancer mortality rates. In fact, the magnitude of the correlation between prostate cancer mortality and milk is greater than for other foods that are high in animal fat (e.g., meats)[4]. Relative to non-drinkers or men who rarely drink milk, men consuming a substantial amount of milk, as well as other dairy products, are at increased risk for prostate cancer in case-control[5-11] and prospective cohort[12-14] studies. The results indicate that milk and dairy products increase prostate cancer occurrence or progression. While this association may be related to the fat content of these products, in some cases skim or low-fat milk appear to be risk factors[14-16], suggesting that milk imparts an excess risk beyond that of fat alone.

More recently, a positive association between calcium intake and prostate cancer risk has been postulated[14]. This relation may be indirectly inferred in studies of skim or low-fat milk and dairy consumption, the primary source of calcium in most countries. A U.S. prospective cohort study[14] and a Swedish case-control study[11] found a positive association between calcium intake and prostate cancer risk. In the cohort study[14], both dietary and supplemental sources of calcium were independently associated with increased prostate cancer risk, suggesting that the calcium component of dairy foods, rather than some other aspect, confers the elevated risk. The risk elevation was apparent particularly in doses higher that 2000 mg of calcium per day. Further study is required to establish the optimal calcium intake for middle-aged to elderly men, taking into account overall health status related to high calcium intake.

Micronutrients

Tomato Products and Lycopene

Lycopene is a carotenoid that cannot be converted into vitamin A and that is found primarily in tomatoes. Lycopene, which confers the red color to tomatoes, is the most efficient carotenoid in quenching potentially cancer-enhancing free radical reactions[17]. Several prospective epidemiologic studies have

evaluated tomato or lycopene intake in relation to prostate cancer risk. A potential benefit of tomatoes was first observed in Seventh-day Adventist men[18]. In a larger study, the Health Professionals Follow-up Study[19], intake of β-carotene was not associated with risk of prostate cancer, but high intake of lycopene was related to a statistically significant 21% reduction in risk. Also, high intake of tomatoes and tomato products, which accounted for 82% of lycopene, was associated with a 35% lower risk of total prostate cancer, and a 53% lower risk of advanced (extraprostatic) prostate cancer. Of the individual items, tomato sauce had the greatest benefit. Two to three servings per week lowered risk by about 40%. Interestingly, due to the cooking in oil, the lycopene from tomato sauce is much better absorbed into the body. Another study conducted in Athens, Greece, also found little benefit from raw tomato consumption and a much greater benefit with cooked tomatoes[20].

Recent results from the Physicians' Health Study[21] of aggressive prostate cancer (extraprostatic of Gleason grade ≥7 or poorly differentiated) found a statistically significant 44% lower risk when comparing high to low quintile of plasma lycopene. Another study conducted in a Japanese-American population in Hawaii did not find an association, but the lycopene level was three-fold lower than in the Physicians' Health Study[22].

Overall, the epidemiologic data strongly indicate that intake of tomatoes and tomato products may lower risk of prostate cancer. This benefit may be related to lycopene, but other potential beneficial substances instead of or combined with lycopene cannot be excluded. Definitive proof for lycopene may await a randomized trial, but the available data suggest that adequate consumption of tomato and tomato-based products may be prudent. This recommendation is consistent with current guidelines to increase fruit and vegetable consumption to lower risk of cancer and other health-related conditions. The specific use of lycopene-concentrated pills, however, needs to be evaluated in trials before recommendations can be made.

Vitamin E

Vitamin E or tocopherol, an essential nutrient with antioxidant properties, has been proposed to possess anti-cancer properties. Although most epidemiological studies had not supported a role of vitamin E, interest in this relationship has reemerged as a result of a randomized trial of β-carotene and vitamin E in the prevention of cancer in Finnish smokers. In that study, a statistically significant 32% reduction in prostate cancer incidence and a 41% reduction in prostate cancer mortality was observed among the men who were randomized to receive vitamin E supplementation compared to those who received a placebo[23]. It is noteworthy that although many epidemiologic studies had not supported an overall relationship, vitamin E in most studies appeared protective for prostate cancer among smokers[24,21,25]. This pattern is intriguing given that the Finnish trial consisted of smokers suggesting that vitamin E is protective against prostate cancer but only in smokers.

Selenium

Selenium is essential for the activity of glutathione peroxidase, an important antioxidant enzyme[26]. In a randomized study[27,28], a striking 63% reduction in prostate cancer risk was observed among men randomized to selenium relative to a placebo. This study was designed to examine the impact of 200 micrograms of selenium supplementation daily on risk for recurrent skin cancer, and prostate cancer was not a primary endpoint when the study was initiated. Following this report, the relation between selenium status and prostate cancer risk was examined in a case-control study based on toenail selenium level, which estimates the selenium level in the body[29]. This study similarly showed a benefit of high selenium status. Based on these provocative studies, resolving the potential impact of selenium as a preventive agent against prostate carcinogenesis should be a top priority.

Summary

The causes of prostate cancer are complex, involving interactions among genetic, dietary, hormonal, and lifestyle factors. Although our understanding of potentially modifiable causes of prostate cancer is far from desirable, recent studies suggest great promise of potential targets for preventive interventions. Recently identified modifiable factors that eventually may be targets for intervention, but require further investigation, are the benefits of higher intake of tomato products or specifically the carotenoid lycopene, the trace mineral selenium, vitamin E among smokers, and other antioxidants. High intake of red meat and dairy products in particular, and perhaps low fish consumption, has been relatively consistently related to greater risk of prostate cancer. Although fat may underlie these associations, other components of this dietary pattern should also be considered. Based on these important leads, continued research into the potentially modifiable risk factors for prostate cancer should be a top priority.

The Whitehall-Robins Report is a Whitehall-Robins publication that focuses on current issues on the role of vitamins and minerals in health promotion and disease prevention. Complimentary copies are distributed to Canadian health care professionals active or with a special interest in nutrition. Each issue is written and/or reviewed by independent health care professionals with expertise in the chosen topic.

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