Milk Consumption and Prostate Cancer

PHYSICIANS COMMITTEE FOR RESPONSIBLE MEDICINE

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Abstract

Prostate cancer is one of the most common malignancies worldwide, with an estimated 400,000 new cases diagnosed annually. Its incidence and mortality have been associated with milk or dairy product consumption in international and interregional correlational studies. As a result, case-control and cohort studies have further investigated this association and are described in this review. Of twelve case-control studies, six found significant associations, as did five of eleven cohort studies, with relative risk of prostate cancer among those with the most frequent dairy product consumption ranging between 1.3 and 2.5, with evidence of a dose-response relationship. Mechanisms that may explain this association include the deleterious effect of high-calcium foods on vitamin D balance, the tendency of frequent dairy intake to increase serum insulin-like growth factor I (IGF-I) concentrations, and the effect of dairy products on testosterone concentration or activity.

Introduction

Prostate cancer is the fourth most common malignancy among men worldwide, with an estimated 400,000 new cases diagnosed annually, accounting for 3.9 percent of all new cancer cases.[1] Epidemiologic evidence strongly suggests that dietary factors play a major role in prostate cancer progression and mortality, with protective effects associated with consumption of fruit (particularly tomatoes), vitamin E, and selenium, and increased risk linked to dairy products, meat, and fat.[2] Dairy product consumption has been associated with prostate cancer risk in divergent populations, and several studies have investigated mechanisms that may explain these findings. This review describes studies reporting prostate cancer risk in relation to milk or dairy products generally. It does not include studies reporting only intake of individual milk derivatives, such as butter, or nutrients, such as fat.

Correlational Studies

In international and interregional correlational studies, dairy product consumption has been consistently associated with prostate cancer mortality.[3-7] The largest and most recent of these, based on World Health Organization mortality figures for 1985-1989 from 59 countries and United Nations food balance data for 1979-1981, reported a strong correlation between per capita milk consumption and prostate cancer mortality ($r = 0.78$, $P<0.0001$).[7] A more geographically restricted study, conducted in 20 Italian regions, found a similar correlation between prostate cancer mortality and milk consumption ($r = 0.75$, $P <0.01$).[6]

International correlational studies typically rely on food "disappearance" data, which may not accurately reflect intake, and are limited in their ability to control for potential confounders. They are also subject to variability in reporting practices, although this is less likely to influence mortality data than incidence figures. Some of the weaknesses of international correlational studies are avoided in case-control and cohort studies. Case-control studies compare the recalled diets of individuals with cancer to those of individuals without cancer who are similar in other relevant respects. Because cases and locally recruited controls are likely to have similar dietary patterns, the sensitivity of such studies is often limited. Cohort studies gather dietary information from healthy volunteers who are then followed over time.

Case-Control Studies

Six case-control studies in geographically diverse areas have reported significantly increased risk of prostate cancer (relative risk ranging from 1.5 to 2.5) for those in the highest categories of dairy product consumption, compared to lower consumption levels (Table 1).[8-13] Four additional studies reported nonsignificant positive associations, and two found no association between dairy product consumption and prostate cancer incidence.[14-19]

Two studies in northern Italy compared prostate cancer patients to hospital controls, finding increased risk of prostate cancer among those with the most frequent milk consumption.[8-10] Similarly, a study at Roswell Park Memorial Institute in Buffalo, NY, found an increased risk of prostate cancer with the daily consumption of three or more glasses of whole milk, compared to never drinking milk.[9] In Montevideo, Uruguay, a comparison of prostate cancer patients to hospital controls, most of whom had other forms of cancer, found an increased risk of prostate cancer associated with drinking two or more milk servings per day, compared to having less than one serving per day.[11] In Örebro county, Sweden, men with prostate cancer were compared to controls selected from a population register. Higher dairy product consumption was associated with increased relative risk of prostate cancer.12A preliminary study from a portion of this patient sample found no associations between prostate cancer and any food recalled as having

been consumed during adolescence.[20] A U.S. study compared men newly diagnosed with prostate cancer and healthy population-based controls in Georgia, New Jersey, and Michigan. Dairy product consumption was associated with prostate cancer risk among whites, but not blacks.[13]

These studies have the methodologic strengths of statistical adjustment for age and other factors and reasonably large sample sizes (Table 1). Of those studies finding positive but nonsignificant associations between dairy use and prostate cancer, several used smaller sample sizes or failed to adjust for age or other variables (Table 1). In Los Angeles and Chicago, prostate cancer patients were matched to hospital controls, finding nonsignificant increases in dairy product consumption among cancer patients.[14] A Minnesota study comparing prostate cancer patients with hospital and neighborhood controls reported nonsignificant increases in dairy product consumption among cancer patients.[15] Similarly, a small study in Japan comparing prostate cancer patients to healthy controls from a prostate cancer-screening program found a nonsignificant increased risk associated with daily milk consumption.[16] In Athens, Greece, prostate cancer patients were compared to hospital controls. Milk and dairy product consumption was marginally positively associated with prostate cancer risk.[17]

A Swedish case-control study including men with prostate cancer and unrelated controls drawn from a twin registry found no relationship between cancer risk and any dietary factor.[18] An English study compared prostate cancer patients to controls with benign prostatic hyperplasia (BPH) and hospital controls with non-urological disease; data for both groups of controls were combined. The study reported no association between dairy product consumption and prostate cancer risk. The use of BPH patients as controls in this study may have reduced its sensitivity, as BPH may have antecedents similar to those of prostate cancer.[19]

Cohort Studies

Five of eleven cohort studies have found significant associations between milk or dairy product consumption and prostate cancer incidence or mortality.[21-25] Six studies found no association between milk or dairy product use generally and prostate cancer incidence or mortality.[26-31]

A 20-year study of prostate cancer mortality among California Seventh-day Adventists reported a dose-related increased risk of age-adjusted prostate cancer mortality with milk consumption (for >3 glasses daily, RR = 2.4, 95% CI, 1.3-4.3; for 1-2 glasses daily, RR = 1.8, 95% CI, 1.0-3.0, compared to <1 glass per day.) In a multivariate analysis adjusting for age, education, body weight, and consumption of meat, milk, cheese, and eggs, the relative risk of fatal prostate cancer associated with drinking >3 glasses of milk per day was reduced to 1.5 and was no longer statistically significant ($p<0.10$).[21] However, adjustment for cheese consumption may be inappropriate if the relevant dietary factor is dairy product consumption generally. Similarly, adjustment for body weight may be inappropriate if increased body weight is one of the mechanisms by which dairy product consumption influences prostate cancer risk. A separate study of California Adventists studied cancer incidence, rather than mortality, finding no relationship with milk consumption.[27]

A dose-response relationship was also suggested by a cohort study including various ethnicities in Hawaii. Relative risks of prostate cancer, adjusted for age, ethnicity, and income, for men in the middle and highest tertiles of milk consumption were 1.3 (CI, 1.0–1.9) and 1.4 (CI, 1.0-2.1), respectively, compared to the lowest tertile. Although these 95% confidence intervals included 1.0, a statistically significant trend was reported (Ptrend = 0.04).[22]

In the Health Professionals Follow-Up Study, a cohort of U.S. male dentists, optometrists, osteopaths, pharmacists, and veterinarians, relative risk of advanced prostate cancer associated with daily consumption of more than two glasses of milk, compared to zero, was 1.6 (95% CI, 1.2-2.1, Ptrend = 0.002). For metastatic disease, relative risk was 1.8 (95% CI, 1.2-2.8, Ptrend = 0.01). Of the milk consumed, 83% was skim or low-fat.[23]

The Netherlands Cohort Study reported a trend of increased prostate cancer risk with increasing milk consumption after adjustment for age, family history of prostate cancer, and socioeconomic status, although the difference in risk, compared to the lowest (index) quintile of milk consumption, was significant only for the 4th quintile (RR= 1.63, 95% CI, 1.20-2.20, Ptrend = 0.02).[24]

In the Physicians' Health Study cohort, consumption of two and one-half dairy servings daily was associated with increased risk of prostate cancer, compared to having less than one-half serving daily, after adjustment for age, smoking, exercise level, and body mass index (BMI).[25]

Among the studies finding no association between dairy product use and prostate cancer, one, conducted in Norway, found a significantly increased age-adjusted risk of prostate cancer with consumption of skim milk, compared to whole milk (incidence rate ratio 2.2, 95% CI, 1.3-3.7), although milk consumption in general was not associated with risk. The authors speculate that the relatively young age of their sample (mean age 43 years, range 16-56 years, at the outset of a 9- to15-year follow-up period) may have reduced study sensitivity.[31]

Hirayama found a protective effect of green and yellow vegetables, but no detectable effect of milk consumption. Although the cohort was large (112,261 men), it identified only 63 cancer deaths during the follow-up period, and did not limit the inclusion of the oldest participants. Milk consumption was probably uncommon in this group, but the number of men consuming milk with various frequencies was not reported.[26] In a cohort of men of Japanese ancestry living in Hawaii, there was no association between milk consumption and age-adjusted prostate cancer risk. Milk consumption was uncommon; only 34% of cases consumed milk five times per week or more.[28] In a Rancho Bernardo, California, cohort (aged 50-84 at the study's outset), no relationship was

found between whole milk consumption and prostate cancer incidence during 14-year follow-up, after adjustment for age, history of heart disease or diabetes, BMI, systolic blood pressure, smoking, and plasma cholesterol concentration. Milk consumption averaged 0.5 cups per day.[29] In a cohort of white male policyholders of the Lutheran Brotherhood Insurance Society, most of whom lived in Minnesota and the northeastern U.S., no associations were identified between prostate cancer mortality and any dietary factor. The authors cautioned that the lack of an association between dietary factors and cancer risk may be partially due to the limited number of items in the food-frequency questionnaire and the homogeneous nature of the cohort, heavily weighted toward individuals of Scandinavian descent.[30]

In summary, six of twelve case-control studies and five of eleven cohort studies found significant associations between milk or dairy product consumption and prostate cancer incidence and mortality. Particularly among cohort studies, those reporting significant associations were generally larger and more recent.

Mechanisms

Dairy products may influence the incidence or progression of prostate cancer by several possible mechanisms. One for which evidence is particularly compelling is the

effect of high-calcium foods on vitamin D metabolism. In several prospective studies, calcium intake has emerged as an independent predictor of prostate cancer risk.[12,23,25] Vitamin D is derived either by conversion from 7-dehydrocholesterol in a reaction catalyzed by ultraviolet light, or from dietary sources. For conversion to the biologically active hormone, a hydroxyl group is added in the liver to form 25(OH) vitamin D, and a second hydroxyl group is added in the kidney, producing 1,25(OH)2 vitamin D.

Vitamin D receptors are present on prostate epithelium. Among other functions, 1,25(OH)2 vitamin D reduces cell proliferation and enhances cell differentiation.[32] An oral calcium load suppresses parathyroid hormone secretion which, in turn, reduces renal 1,25(OH)2 vitamin D production. Calcium itself also downregulates this reaction. Although some dairy products are supplemented with vitamin D, this inactive prehormone does not appreciably increase 1,25(OH)2 vitamin D blood levels, and the net effect of dairy consumption is a reduction in blood levels of this active form of the hormone. Milk's high content phosphorus and animal protein may aggravate this effect.[32]

Dairy product consumption has also been shown to increase serum concentrations of insulin-like growth factor (IGF-I).[33,34] In in-vitro studies, IGF-I has mitogenic and antiapoptotic properties on prostate epithelial cells.[35,36] Case-control studies in diverse populations have shown a strong and consistent association between serum IGF-I concentrations and prostate cancer risk.[37] In men and women aged 55 to 85 years, the addition of 3 daily eight-ounce servings of nonfat or 1% milk for 12 weeks was associated with a 10% increase in serum IGF-I concentration ($P<0.001$).[34] Mean serum IGF-I concentration among vegans was shown to be 8 percent lower than among ovolactovegetarians ($P=0.01$) and 9 percent lower than among meat-eaters ($P=0.01$).[38] Changing dietary protein sources from animal sources to plant sources has been shown to reduce serum IGF-I concentrations.[39]

Most dairy products contain substantial amounts of fat and are devoid of fiber, a combination that is likely to increase serum testosterone concentration and activity, with a mitogenic effect on prostate tissue.[40] However, several studies have found an association of dairy product intake with prostate cancer incidence and mortality that is independent of total fat intake and other dietary variables.[25,40,41]

Dietary factors other than dairy products are also associated with risk. Generally speaking, diets high in animal products are associated with higher risk, while those rich in plant foods, particularly tomatoes, are associated with reduced risk.[2] Daily soymilk consumption was associated with a significant reduction in prostate cancer risk in a cohort of 13,855 Seventh-Day Adventist men (RR = 0.3, 95% CI, 0.1-1.0, compared to those never drinking soymilk).[42] Isoflavones in soymilk inhibit growth of human prostate cancer cells and also inhibit 5a-reductase, an enzyme that converts testosterone to 5a-dihydrotestosterone in the prostate.[42] A similar beneficial effect was demonstrated for tofu consumption.[28] Based on experience with a case-control study in Athens, Greece, researchers calculated that the combined effect of reducing dairy consumption, substituting olive oil for other added fats, and increasing tomato intake to the levels consumed by those in the lowest risk categories could reduce prostate cancer risk in their population by 41 percent (95% CI, 23-59%).[43]

Conclusions

Evidence from international, case-control, and cohort studies suggests that men who avoid dairy products are at lower risk for prostate cancer incidence and mortality, compared to others. In case-control and cohort studies, the relative risk of prostate cancer among subgroups with the most frequent milk consumption, compared to those at the lowest consumption levels, falls in the range of 1.3 to 2.5. These findings raise two important questions: Does the observed relationship represent cause and effect, and is available evidence sufficient to justify a recommendation that milk-drinking men alter their dietary habits?

Findings supporting a cause-and-effect relationship include the relative consistency of this association in diverse populations, evidence of a dose-response relationship, plausible biological mechanisms that underlie the observed associations, and no reasonable alternative explanation for these findings. Perspective is lent to the second question by a comparison with evidence linking alcohol use and breast cancer risk. Although somewhat fewer studies have addressed the association between milk and prostate cancer, their demonstrated effect strength and consistency of evidence approach those relating alcohol to breast cancer risk, an association that is now widely

accepted and incorporated into the Dietary Guidelines for Americans.[44] A pooled analysis of cohort studies showed that the adjusted relative risk of incident breast cancer for women consuming 2-5 drinks (30-60 grams of alcohol) per day was 1.41 (95% CI, 1.18-1.69).[45] In a 1997 review by the World Cancer Research Fund and the American Institute for Cancer Research, six of eleven cohort studies and fifteen of thirty-six case-control studies found such an association.[46]

Men who choose to avoid dairy products reap other nutritional benefits, such as a reduction in total fat, saturated fat, and cholesterol intake. Unless they replace dairy products with calcium-fortified products or calcium supplements, they are likely to reduce their calcium intake in the process. However, a reduction in calcium intake may be an important mechanism by which reducing or avoiding dairy products reduces prostate cancer risk. Moreover, there is no apparent risk to moderate reductions in calcium intake. There is little evidence to suggest that a high intake of calcium from dairy or other sources reduces the risk of osteoporotic fractures among men. Few studies have examined the effect of dietary calcium on osteoporosis risk in adult men independently of vitamin D intake.[47] There has been some indication that a higher intake of calcium, including that from dairy sources, in the context of an omnivorous American diet, is associated with reduced recurrence of colonic adenomatous polyps.[48] However, in Africa, in the context of a low-calcium, low-dairy diet, both adenomatous polyps and colon cancer are much rarer than in Western countries.[49] Some studies suggest that calcium, including that in dairy products, may reduce blood pressure, but the effect, if any, is small (on the order of <2 mm Hg systolic and <1 mm Hg diastolic), far smaller than the effect of adding vegetables and fruits to the diet.[50-51]

In conclusion, several lines of evidence indicate that consumption of dairy products is associated with increased risk of prostate cancer incidence and mortality. Avoidance of these products may offer a means of reducing risk of this common illness.

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Table 1. Case-Control Studies of Dairy Product Intake and Prostate Cancer

Author, Year, Location	No. of Cases	Findings Related to Dairy Intake RR (95% CI), where applicable	Ajustment			
			Age	Location	Weight	Other
Rotkin, 1977, USA	111	Cases consumed more dairy (ns)	n	n	n	n
Schuman et al., 1982, USA	240	Cases consumed more dairy (ns)	n	n	n	n
Mishima et al., 1985, Japan	100	Cases consumed more dairy (ns)	n	n	n	n
Talamini et al., 1986, Italy	166	milk/dairy>5/wk vs less often 2.5 (1.3-4.7)	y	n	y	y
Mettlin et al., 1989, USA	371	milk 3 servings/d vs none 2.49 (1.27-4.87)	y	y	n	n
Talamini et al., 1992, Italy	271	milk>10/wk vs <2/wk 1.58 (1.06-2.36)	y	y	y	y
De Stefani et al., 1995, Uruguay	156	milk>2 servings/d vs <1/d 1.7 (1.1-2.9)	y	y	n	n
Hayes et al., 1996, USA	483 white 449 black	milk: h vs 1 quartile 1.7 P=0.03 milk: h vs 1 quartile 0.9 P=0.75	y n	y n	n n	n n
Grönberg et al., 1996, Sweden	406	milk: >5 servings/d vs 0 servings/d 0.84 (0.44-1.57) Ptrend=ns	y	n	n	n
Ewings et al., 1996, UK	159	>7 pints/wk (ns) vs <3 pints/wk 0.95 (0.50-1.83)	y	n	n	n
Chan et al., 1998b, Sweden	526	dairy>4.5 servings/d vs <2.5 servings/d 1.49 (1.01-2.19)	y	n	y	n
Tzonou et al., 1999, Greece	320	quintile trend 1.6 P=0.12	y	n	y	y

Table 2. Cohort Studies of Dairy Product Intake and Prostate Cancer

Author, Year, Location	Size of Cohort Cases/Death	Findings Related to Dairy Intake RR (95% CI), where applicable	Ajustment			
			Age	Location	Weight	Other
Hirayama, 1979, Japan	112,261 63 deaths	milk daily vs rarely or never (ns)	n	n	n	n
Snowdon et al., 1984, USA	6,763 99 deaths	milk>3 servings/d vs <1/d 2.4 (1.3-4.3) (multivariate: 1.5, P<0.10)	y y	n n	n y	n y
Mills et al., 1989, USA	14,000 180 cases	milk>daily vs never 0.80 (0.54-1.19)	y	n	y	y
Thompson et al., 1989, USA	1,776 100 cases	per cup/d 1.0 (0.9-1.2)	y	n	n	n
Severson et al., 1989, USA	7,999 174 cases	milk>5 servings/wk vs <1 serving/wk 1.00 (0.73-1.38)	y	n	n	n
Hsing et al., 1990, USA	17,633 149 deaths	dairy>86 servings/mo vs <26 servings/mo 1.0 (0.6-1.7)	y	n	n	y
LeMarchand et al., 1994, USA (Hawaii)	20,316 198 cases	milk, high vs low tertile 1.4 (1.0-2.1)	y	n	n	y
Veierød et al., 1997, Norway	25,708 72 cases	milk, not quantified (na)	y	n	n	n
Giovannucci et al., 1998a, USA	47,781 1,369 cases	milk>2 servings/d vs none 1.6 (1.2-2.1)	y	n	y	y
Schuurman et al., 1999, Netherlands	58,270 642 cases	milk, high vs low quintile 1.12 (0.81-1.56) Ptrend=0.02	y	n	n	n
Chan et al, 2000, USA	20,885 1,012 cases	dairy>2.5 servings/d vs <0.5 serving/d 1.34 (1.04-1.71)	y	n	y	y