Lactase Persistence, Dietary Intake of Milk, and the Risk for Prostate Cancer in Sweden and Finland

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Abstract

Prostate carcinoma is the most common cancer in men. Its primary pathogenesis is mostly unknown. Dairy products containing lactose have been suggested to be risk factors for prostate cancer. Digestion of lactose is dependent on lactase activity in the intestinal wall. A single nucleotide polymorphism C to T residing 13,910 bp upstream of the *lactase* gene has been shown to associate with the developmental down-regulation of lactase activity underlying persistence/non-persistence trait. To find out whether lactase persistence is related to the risk for prostate cancer, we genotyped 1,229 Finnish and 2,924 Swedish patients and their 473 Finnish and 1,842 Swedish controls using solid-phase minisequencing. To explore if dairy products have an association with prostate cancer, we analyzed the milk consumption in the Swedish study consisting of 1,499 prostate cancer patients and 1,130 controls (Cancer Prostate in Sweden I study) using a questionnaire. Only the consumption of low-fat milk was found to be associated with increased risk of prostate cancer [odds ratio (OR), 1.73; 95% confidence interval (95% CI), 1.16-2.39]. A statistically significantly higher ($P < 0.01$) lactose intake was observed among subjects with high lactase activity (C/T and T/T genotypes) compared with those with low lactase activity (C/C genotype). Lactase persistence did not associate with increased risk for prostate carcinoma in the Finnish (OR, 1.11; 95% CI, 0.83-1.47; $P = 0.488$) or in the Swedish populations (OR, 1.16; 95% CI, 0.91-1.46; $P = 0.23$). In conclusion, lactase persistence/nonpersistence contains no risk for prostate cancer. Analysis of different milk products showed some evidence for low-fat milk as a potential risk factor for prostate cancer. (Cancer Epidemiol Biomarkers Prev 2007;16(5):956–61)

Introduction

Prostate cancer is the most common malignancy among men in developed countries (1). Both endogenous factors (family history, hormones, ethnicity, and oxidative stress) and exogenous factors (nutrition and lifestyle) have been suggested as risk factors but the primary etiology is thus far unknown. High dairy product intake has been associated with an increased risk of prostate cancer in case-control as well as cohort studies (2-7). In two recent meta-analyses, high intakes of dairy products and calcium were associated with a slightly increased risk of prostate cancer (4, 8). In Scandinavian countries, prostate cancer is the most frequently diagnosed cancer in men (9, 10); likewise, the consumption of dairy products is the highest in the world (11).

Lactose is the main sugar of milk that is digested by the lactase enzyme to glucose and galactose in the intestinal wall. Lactase enzyme activity is high at birth but down-regulated after weaning in most of the world's populations, the condition called adult-type hypolactasia or lactase nonpersistence (12). A mutation has occurred in human history that has made some humans able to digest lactose throughout life (lactase persistence), and this mutation is particularly common in the populations in the Nordic countries. The diagnosis of low lactose absorbing capacity has been based on lactose tolerance test or breath hydrogen test with varying specificity and sensitivity (13). Data are contradictory about the effect of lactase enzyme activity on the absorption of calcium in milk: decreased calcium absorption has been reported in lactase-deficient subjects (14); however, contrary data has also been presented (15, 16).

A single nucleotide polymorphism C/T_{-13910} (rs4988235), residing 13,910 bp upstream of the lactase-encoding gene (*LCT*), has been shown to associate with lactase persistence/nonpersistence trait (17). Many functional studies have shown that the C/T_{-13910} variant regulates the expression of the *LCT* gene (17-22). The C/T_{-13910} genotype defines lactose malabsorbers (lactase activity <10 units/g protein) and the C/T_{-13910} and T/T_{-13910} genotypes define lactose absorbers (lactase activity $\geq$10 units/g protein), meaning that C/T_{-13910} and T/T_{-13910} genotypes always have normal lactase activity, whereas C/C_{-13910} genotype always has a declined lactase activity (17, 18, 21, 23). The C/T_{-13910} variant is the major variant of lactase persistence/nonpersistence in North European populations. Several other variants close to the C/T_{-13910} variant has been recently identified in African populations (24, 25). However, their correlation with lactase activity remains to be clarified.

We hypothesize that the high incidence of prostate cancer in the Nordic countries is partially driven by high dairy (milk) intake, explained by the high prevalence of lactase persistence in our populations. This study addresses the question of whether there exists an association between the C/T_{-13910} genotypes reflecting lactase activity and the risk of prostate

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Table 1. Selected baseline characteristics of prostate cancer cases and controls in the Swedish CAPS and Finnish studies

Characteristics	Sweden		Finland	
	Controls	Cases	Controls	Cases
Age, mean (y)	67.3	65.9	NA	69.0
BMI, mean (kg/m^2)	26.2	26.3	—	—
Education, *n* (%)				
Compulsory school 0-9 y	352 (45)	619 (45)	—	—
Upper secondary 10-12 y	334 (43)	544 (40)	—	—
University ≥13 y	96 (12)	194 (14)	—	—
Missing	5 (0.6)	5 (0.4)	—	—
Country of birth, *n* (%)				
Sweden	731 (93)	1,295 (95)	—	—
Other European countries	49 (6)	62 (4.6)	—	—
Missing	7 (0.9)	5 (0.4)	—	—
Smokers, *n* (%)				
Never	297 (38)	528 (39)	—	—
Ever	478 (61)	815 (60)	—	—
Missing	12 (1)	19 (1)	—	—
Prostate cancer stage, *n* (%)*				
Localized	—	1,570 (56)	—	677 (55)
Advanced	—	1,193 (42)	—	552 (45)
Unknown	—	53 (2)	—	0

Abbreviations: NA, not available; BMI; body mass index.
*See Materials and Methods for definition of prostate cancer stage.

cancer in Finland and Sweden. In the Swedish study population [Cancer Prostate in Sweden (CAPS) I], detailed exposure information on dairy product intake was available and we studied the association between milk intake and the risk for prostate cancer. In addition, we investigated if the C/T_{-13910} single nucleotide polymorphism of lactase persistence affected milk intake in the general population.

Materials and Methods

Study Population. Baseline characteristics among the study participants of CAPS and Finnish study populations are presented in Table 1. CAPS is a population-based, case-control study of prostate cancer etiology. The study design and exposure assessment have been described in detail elsewhere (26). Cases were all men between 35 and 79 years of age with pathologically verified adenocarcinoma of the prostate (ICD-10, C61) reported to four regional cancer registries in Sweden. Clinical data were obtained from linkage to the National Prostate Cancer Registry (27) for 95% of patients in the study. Control subjects were randomly selected from the Swedish Population Registry, and frequency was matched to the expected distribution of the cases by age (in 5-year categories) and geographic residence. Advanced cases were defined as those with at least one of the following criteria: tumor-node-metastasis stage, T_3/T_4, N_+, M_+; Gleason score 8 to 10; or prostate-specific antigen level, ≥100 ng/mL (28). Localized cases were those not meeting any of the above criteria.

The CAPS study was divided into two substudies, with enrollment between January 1, 2001, and September 30, 2002, for the first part (CAPS I), and between October 1, 2002, and October 31, 2003, for the second part (CAPS II). The study population of the whole CAPS was ethnically homogeneous, and most (>95%) of the men were born in Sweden. Participants in CAPS I answered an extensive questionnaire concerning dietary habits. Of 1,895 invited prostate cancer cases, 1,499 (79%), and of 1,684 invited controls, 1,130 (67%), agreed to participate by completing the questionnaire. Of the cases, 1,400 (74%) donated a blood sample and 1,352 (71%) both completed the questionnaire and donated blood. Of the controls, 879 (52%) donated blood and 858 (51%) did both. In CAPS II, the response rates were 1,524 of 2,037 (75%) among prostate cancer cases and 963 of 1,456 (66%) among the controls who agreed to participate by donating a blood sample.

The Finnish material consisted of 1,229 unselected, consecutive patients with prostate cancer with the mean age of 69.0 years (range 45-94 years). The DNA samples from unselected consecutive prostate cancer patients were collected from patients diagnosed with pathologically verified prostate cancer during 1999 to 2002 at the Tampere University Hospital, which serves as a regional referral center in the area for all patients with prostate cancer. Thus, we obtained a population-based collection of patients. For the Finnish subjects with prostate cancer, clinical characteristics collected include age, prostate-specific antigen, tumor-node-metastasis stage, WHO grade, and Gleason score. The population controls consisted of 473 DNA samples from anonymous, voluntary, and healthy male blood donors (18-65 years old) from the same region, obtained from Blood Center of the Finnish Red Cross in Tampere.

The study protocol was accepted by the local ethical committees and written informed consent was obtained from all study participants in both the Finnish and Swedish studies.

Dietary Assessment. The self-administered questionnaire assessed known and potential risk factors for prostate cancer (24). The questionnaire included a validated food frequency questionnaire to measure average intake of foods and beverages during the preceding year (29). Participants were asked how much, on average, they drank low-, medium-, or high-fat milk and low- or high-fat yoghurt/sour milk (glasses per day), and how much they ate low-fat cheese, high-fat cheese, cottage cheese, or melted cheese (slices per day). They were also asked how often, on average, they ate cream (12% or 40% fat), crème fraîche (17% or 34% fat), mayonnaise (32% or 80% fat), ice cream or chocolate: never, once to thrice per month, once to twice per week, three to four times per week, five to six times per week, once per day, twice per day, or thrice or more per day. Questionnaire data about the average intake of food items were converted into average intake of energy and nutrients by linkage to the database for nutrients created by the Swedish National Food Administration (30).

Genotyping. Genotyping was done as described earlier by Enattah et al. (17). Shortly, the DNA fragment spanning the C/T_{-13910} variant was amplified by PCR (primer sequences available on request), and two parallel minisequencing reactions were carried out for each PCR product. Each sample plate contained two blank wells and two control samples of known lactase genotypes for quality control.

Statistical Methods. Baseline characteristics of cases and controls were compared using a two-sided *t* test for continuous variables, and a χ^2 test for categorical variables. The association between intake of milk products and prostate cancer was summarized in terms of odds ratios (OR), an estimate of the incidence rate ratio, and corresponding 95% confidence intervals (95% CI), and it was evaluated by age- and energy-adjusted unconditional logistic regression. The multivariate nutrient density model was used (31). Participants with extremely high or low energy intake (<2,100 or >21,000 kJ/d) were excluded from the analysis (n = 16). Total intake of milk was grouped into never-ever drinkers or into three categories (none, one to three glasses per day, and three glasses or more per day). A variable was created from a group of dairy products rich in lactose by summing the intake of milk, yoghurt/soured milk, chocolate, ice cream, and low-fat cream (12% fat). Moreover, a variable for dairy products low in lactose was created by summing the intake of cheese, cottage cheese, melted cheese, crème fraîche, and high-fat cream (40% fat), then categorizing the total into quartiles based on the distribution among the controls.

As mentioned above, age- and energy-adjusted models (with age in 5-year intervals and total energy intake as a continuous variable) were fitted, as well as models were adjusted for potential confounding factors. The selection of covariates

Table 2. Genotype frequencies and ORs with 95% CIs for prostate cancer among the C/T$_{-13910}$ genotypes

Study	Genotypes	Frequencies, *n* (%)		OR (95% CI)	Frequencies, *n* (%)	OR (95% CI)	Frequencies, *n* (%)	OR (95% CI)
		Controls	All cases	All cases	Advanced		Localized	
Finnish	CC	82/473 (17.3)	196/1,229 (15.9)	1.00 (reference)	91/552 (16.5)	1.00 (reference)	105/677 (15.5)	1.00 (reference)
	TT/TC	391/473 (82.7)	1,033/1,229 (84.1)	1.11 (0.83-1.47)	461/552 (83.5)	1.06 (0.77-1.47)	572/677 (84.5)	1.14 (0.83-1.57)
Swedish CAPS I +II	CC	128/1,673 (7.6)	192/2,797 (6.9)	1.00* (reference)	71/1,183 (6)	1.00* (reference)	120/1,562 (7.7)	1.00* (reference)
	TT/TC	1,545/1,673 (92.4)	2,605/2,797 (93.1)	1.16* (0.91-1.46)	1,112/1,183 (94)	1.29* (0.95-1.75)	1,442/1,562 (92.3)	1.03* (0.79-1.35)

*Adjusted for age (in 5-year categories) and geographic residence.

included in the final multivariate models was based on proportional (≥10%) change in β coefficients and previous subject matter knowledge. All covariates included in the final models were considered to be important confounding factors for the relation between the main exposure and prostate cancer, and are listed in the table footnotes. The Hosmer-Lemeshow goodness-of-fit test was used to assess the fit of the model (32).

To explore whether the subjects with the C/C$_{-13910}$ genotype reflecting adult type hypolactasia/lactase nonpersistence less likely drank milk than subjects with lactase persistence allele (T$_{-13910}$) in CAPS I study, age-adjusted binary regression with a logarithmic link was done to estimate risk ratios and corresponding 95% CIs for current status of dairy consumption (milk drinker versus non–milk drinker) or consumption of products high in lactose (high intake versus low intake). Binary regression is a generalized linear model for the binomial family. All analyses in the CAPS study were done using the STATA System Software, version 8.2.

Association between the C/T$_{-13910}$ genotypes and prostate cancer risk was evaluated by unconditional logistic regression analysis. Association with clinical and pathologic features of the disease were tested among unselected cases by the Mann-Whitney test (prostate-specific antigen value at diagnosis; median value was used), Fisher's exact test (tumor-node-metastasis stage, WHO grade, and Gleason score), and independent samples *t* test (age). All analyses in the Finnish study were done by using the SPSS 12.0 statistical software package.

Results

Lactase persistence had no significant effect on the risk of prostate carcinoma in the Swedish study (OR, 1.16; 95% CI, 0.91-1.46; $P = 0.23$) or in the Finnish study (OR, 1.11; 95% CI, 0.83-1.47; $P = 0.488$; Table 2). In the Swedish subjects with prostate cancer, the frequency of the lactase persistence (genotype C/T$_{-13910}$ or T/T$_{-13910}$) was 92.4% and in controls 93.1%. The frequencies of lactase persistence of Finnish cases and controls were 84.1% and 82.7%, respectively (Table 2). We repeated all analyses separately for cases with localized or advanced prostate cancer, and the estimates were similar across disease stages (Table 2). No correlation was seen to any of the clinical variables (data not shown).

Table 3. Relative risk of prostate cancer in association with estimated intake of dairy products estimated as OR with 95% CI, the Swedish CAPS I study

Dietary intake	Frequency/mean (interquartile range)	Controls (*n*)	Cases, *N*	OR* (95% CI)	OR† (95% CI)
All milk glasses/d	Never	134	164	1.00 (reference)	1.00 (reference)
	>0 to <3	723	977	1.12 (0.87-1.43)	1.16 (0.89-1.51)
	≥3	267	348	1.02 (0.76-1.36)	1.18 (0.85-1.66)
	P for linear trend			0.85	0.37
Low-fat milk glasses/d	Never	845	1,022	1.00 (reference)	1.00 (reference)
	>0 to <3	217	353	1.33 (1.09-1.62)	1.34 (1.08-1.65)
	≥3	62	114	1.43 (1.03-1.98)	1.73 (1.16-2.39)
	P for linear trend			0.001	0.0001
High-fat milk glasses/d	Never	870	1,149	1.00 (reference)	1.00 (reference)
	>0 to <3	197	277	1.11 (0.90-1.36)	1.12 (0.90-1.39)
	≥3	57	63	0.88 (0.61-1.28)	0.91 (0.61-1.37)
	P for linear trend			0.83	0.77
All dairy products‡ g/d·MJ	20 (0-32)	281	396	1.00 (reference)	1.00 (reference)
	43 (33-53)	281	380	0.96 (0.77-1.20)	1.00 (0.78-1.27)
	65 (54-78)	281	362	0.92 (0.74-1.15)	0.98 (0.74-1.29)
	108 (79-321)	281	351	0.91 (0.73-1.13)	1.01 (0.72-1.43)
	P for linear trend			0.35	0.98
Products§ high in lactose (>3 g/100 g), g/d·MJ	18 (0-30)	281	398	1.00 (reference)	1.00 (reference)
	40 (30-50)	281	362	0.91 (0.73-1.13)	0.94 (0.75-1.20)
	62 (51-75)	281	371	0.94 (0.76-1.18)	1.03 (0.79-1.35)
	106 (76-317)	281	358	0.92 (0.74-1.15)	1.05 (0.76-1.46)
	P for linear trend			0.55	0.68
Products‖ low in lactose (<3 g/100 g), g/d·MJ	1 (0-2)	281	321	1.00 (reference)	1.00 (reference)
	3 (2-3)	281	411	1.26 (1.01-1.57)	1.23 (0.98-1.55)
	4 (4-5)	281	405	1.23 (0.98-1.53)	1.21 (0.96-1.53)
	7 (5-21)	281	352	1.04 (0.83-1.31)	1.08 (0.84-1.38)
	P for linear trend			0.83	0.63

*Adjusted for age (in 5-y categories) and total energy intake.
† Adjusted for age (in 5-y categories), total energy intake, dietary intake of fruit, vegetables, saturated fat, alcohol, protein, zinc, vitamin C, selenium, phosphorus, eicosapentaenoic acid, and docosahexenoic acid.
‡ Milk, yoghurt/soured milk, cheese, cottage cheese, crème fraîche, and high- and low-fat cream.
§ Milk, yoghurt/soured milk, chocolate, ice cream, and low-fat cream (12% fat).
‖ Cheese, cottage cheese, melted cheese, crème fraîche, and high-fat cream (40% fat).

Table 4. Dairy products intake stratified by the lactase persistence/nonpersistence alleles, among Swedish CAPS I study population

Dietary intake	Single nucleotide polymorphism C/T_{-13910} *n* (%)*								
	Cases			Controls			Total		
	TT/CT	CC	Total	TT/CT	CC	Total	TT/CT	CC	Total
All milk									
Never	127 (10)	24 (26)	151 (11)	74 (10)	12 (21)	86 (11)	201 (10)	36 (24)	237 (11)
Ever	1,142 (90)	69 (74)	1,211 (89)	656 (90)	45 (79)	701 (89)	1,798 (90)	114 (76)	1,912 (89)
Products † high in lactose (g/d)									
Low (0-444)	649 (51)	66 (71)	715 (52)	361 (49)	34 (60)	395 (50)	1,010 (51)	100 (67)	1,110 (52)
High (445-3,290)	620 (49)	27 (29)	647 (48)	369 (51)	23 (40)	392 (50)	989 (49)	50 (33)	1,039 (48)
Total	1,269 (100)	93 (100)	1,362 (100)	730 (100)	57 (100)	787 (100)	1,999 (100)	150 (100)	2,149 (100)

*Column percentage.
† Milk, yoghurt/soured milk, chocolate, ice cream, low-fat cream (12% fat).

There were also no statistically significant differences between the cases and the controls from the CAPS I study population with regard to smoking history, body mass index, and level of education (data not shown). The relative risk of prostate cancer by the level of dairy product intake in the CAPS I study population is shown in Table 3. High intake of low-fat milk was associated with a significantly increased relative risk of prostate cancer. After multivariate adjustment, the risk of prostate cancer was 73% higher among men who drank three glasses of low-fat milk or more per day, compared with men who never drank low-fat milk. In contrast, we found no association between dietary intakes of total milk, high-fat milk, all dairy products, or dairy products high or low in lactose and the risk of prostate cancer. We repeated all analyses separately for cases with localized or advanced prostate cancer, and the estimates were similar across disease stages (data not shown). However, the increased risk for intake of low-fat milk was more pronounced among advanced cases. The adjusted OR comparing men who drank three glasses of low-fat milk or more per day with never drinkers was 1.8 (95% CI, 1.17-2.9, P_{trend} = 0.003) for advanced cases and 1.5 (95% CI, 0.98-2.3; P_{trend} = 0.01) for localized cases. No data of the diet were available from the Finnish prostate cancer patients and their controls.

The different C/T_{-13910} genotype groups in the Swedish study population were stratified according to the consumption of milk and other dairy products high in lactose (Table 4). Among Swedish hypolactasic subjects, 76% were milk drinkers compared with 90% of those with the genotypes of lactase persistence ($P < 0.01$). Thus, 24% of those with the C/C_{-13910} genotype did not drink milk. Of the subjects with the C/C_{-13910} genotype, 33% had high daily intake of lactose (>445 g of lactose containing products). The probability to be a milk drinker was 15% lower among those with the C/C_{-13910} genotype, compared with the lactase-persistent subjects (C/T_{-13910} or T/T_{-13910} genotype; risk ratio, 0.85; 95% CI, 0.78-0.93) and the probability to a have high intake of lactose-containing products was 31% lower among subjects with the C/C_{-13910} genotype (risk ratio, 0.69; 95% CI, 0.55-0.87; data not shown). The estimates were similar when the analyses were done for controls only. The intake of dairy products among the different C/T_{-13910} genotype groups did not differ between those with prostate cancer and the healthy controls (Table 4). The mean intake of milk was lower among hypolactasic subjects than among lactase-persistent subjects, 221 and 348 g/d, respectively ($P < 0.01$; data not shown).

Discussion

High dairy product intake has been shown to be associated with an increased risk of prostate cancer (2-7); however, the underlying mechanism remains poorly understood. High lactase enzyme activity increases the amount of glucose and galactose concentration in blood in lactase-persistent subjects (genotype C/T_{-13910} and T/T_{-13910}). Malignant cells are known to have accelerated metabolism, high glucose requirements, and increased glucose uptake. High levels of glucose consumption are associated with rapid proliferation of androgen-independent prostate cancer cells (33). In our study, high daily intake of lactose or high lactase activity reflected by the C/T_{-13910} and T/T_{-13910} genotypes showed no association with increased prostate cancer risk among lactose absorbers, indicating that lactose intake is not a risk factor for prostate cancer in the Finnish or Swedish populations. However, this does not exclude other components of milk like hormones and other nutrients as risk factors for prostate cancer. Association between this C/T_{-13910} variant and prostate cancer has not been studied before. However, studies about the association between this variant and other cancers have been done (34, 35).

We observed that high intake of low-fat milk was associated with a significantly increased relative risk of prostate cancer, whereas no association between dietary intakes of total milk, high-fat milk, all dairy products, or dairy products high or low in lactose and risk of prostate cancer was observed. This is an agreement with the results published by Tseng et al. (6), in which low-fat milk, but no high-fat milk, contained risk for prostate cancer. Originally, Giovannucci et al. (36) found milk fats not to be related to increase prostate cancer risk. Later on, also Chan et al. (3) have found skim milk to be the dairy product most strongly associated with prostate cancer risk. They found no association between dairy fat or dairy protein and prostate cancer. However, there are also studies that have not found any differences between consumption of various types of milk on the risk of prostate cancer (5). Milk contains various types of fats and some of them are proposed to promote and some to protect against cancer (37-42). Especially polyunsaturated fatty acids, like conjugated linoleic or linolenic acid, have been found to exert inhibitory effects by inhibiting growth (39-42). Milk phospholipid sphingomyelin may also decrease proliferation and inhibit growth of tumor cells through its active metabolites, sphingosine and ceramide (39-42). If some of the milk fats protect against cancer, this could explain why, in this study, high-fat milk was not associated with increased prostate cancer risk and low-fat milk was. However, milk also contains many other factors such as nutrients, minerals, and hormones that can cause mixed effects on progression of prostate cancer by either suppressing or promoting it (43).

The prevalence of adult-type hypolactasia (genotype CC_{-13910}) was 6.9% in Sweden and 17.3% in Finland (among controls). These frequencies correspond to what has been previously published (17, 35, 44). In total, 89% of the Swedish CAPS I study population consumed milk, which reflects the important role of dairy products in the Scandinavian diet. Of those with the C/C_{-13910} genotype, 76% reported to consume

milk; however, only 33% of them consumed products high in lactose. The high prevalence of milk consumption among hypolactasia subjects in Sweden could be explained by low prevalence of lactase nonpersistence among Swedish and thus lower awareness of it (and milk products) as a cause of abdominal symptoms. Furthermore, the availability of lactose-free products in Sweden is not as high as, for example, in Finland, which makes completely lactose-free diet more difficult to carry out in Sweden. It is noteworthy, however, that lactase nonpersistent subjects can tolerate a couple of glasses milk per day especially with meals, and this condition does not prevent the intake of milk and products high in lactose (45-49).

The strengths of our studies include its population-based design, large size, and complete and rapid case ascertainment. The ethnic homogeneity of our study populations reduces the risk of confounding by population stratification. A small fraction of Finnish control subjects might be affected with prostate cancer at a later age. According to the statistics by the Finnish Cancer Registry, the cumulative crude probability of a prostate cancer diagnosis up to 84 years of age is 8.5% based on current incidence rates. Because the Finnish population is genetically homogeneous (50), the typical problems associated with case-control studies (such as ethnicity matching) are avoided. With the detailed exposure information on dietary dairy intake in the CAPS I study, we were able to distinguish among low-fat and high-fat milk and food items high or low in lactose. We were also able to adjust for other food items and nutrients, any or all of which may influence prostate cancer risk. In the Swedish study material, the strict selection of controls and the association between lactase persistence and prostate cancer did not differ between the two groups, indicating no major influence of bias in the selection of controls.

On the other hand, several limitations may have influenced our results. Measurement error associated with the food frequency questionnaire is unavoidable, possibly leading to misclassification of dietary intake. However, because the possible role of dairy products in prostate cancer development is not well known in the general Swedish population, such misclassification was likely nondifferential between cases and controls, leading to underestimation of the strength of any association. However, intake of low-fat products could be perceived as a generally healthy behavior leading to some overreporting among cases that recently have changed their behavior to drink more low-fat milk instead of high-fat milk, and this could account for the observed positive association with prostate cancer risk. Nevertheless, because the postdiagnostic period was short due to the rapid case ascertainment and intake of milk was reported for the preceding year, we believe that this recall bias is not of great concern.

In summary, our results indicate that lactase persistence, defined by the C/T_{-13910} variant, had no significant effect on the prostate cancer risk in the Finnish or Swedish populations. Instead, we observed that high intake of low-fat milk was associated with a significantly increased relative risk of prostate cancer, whereas no association between dietary intakes of total milk, high-fat milk, all dairy products, or dairy products high or low in lactose and risk of prostate cancer was observed.

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