Cultured milk, yogurt, and dairy intake in relation to bladder cancer risk in a prospective study of Swedish women and men

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ABSTRACT

Background: Findings from epidemiologic studies of the effect of dairy foods (mainly milk) on the risk of bladder cancer have been inconsistent.

Objective: We aimed to examine the association between the intake of cultured milk and other dairy foods and the incidence of bladder cancer in a prospective, population-based cohort.

Design: We prospectively followed 82,002 Swedish women and men who were cancer-free and who completed a 96-item food-frequency questionnaire in 1997. Incident cases of bladder cancer were identified in the Swedish cancer registries.

Results: During a mean follow-up of 9.4 y, 485 participants (76 women and 409 men) were diagnosed with bladder cancer. Total dairy intake was not significantly associated with risk of bladder cancer (≥7.0 servings/d compared with <3.5 servings/d: multivariate rate ratio (RR) = 0.87; 95% CI: 0.66, 1.15; P for trend = 0.33). However, a statistically significant inverse association was observed for the intake of cultured milk (sour milk and yogurt). The multivariate RRs for the highest category of cultured milk intake (≥2 servings/d) compared with the lowest category (0 serving/d) were 0.62 (95% CI: 0.46, 0.85; P for trend = 0.006) in women and men combined, 0.55 (95% CI: 0.25, 1.22; P for trend = 0.06) in women, and 0.64 (95% CI: 0.46, 0.89; P for trend = 0.03) in men. The intake of milk or cheese was not associated with bladder cancer risk.

Conclusion: These findings suggest that a high intake of cultured milk may lower the risk of developing bladder cancer.


INTRODUCTION

Cancer of the bladder is the ninth most common malignancy worldwide (1) and the fifth most common in the United States (2). Cigarette smoking is a major cause of bladder cancer, accounting for ≈50% of cases in high-income countries (3). Other established or potential risk factors include schistosomal infection, occupational exposure to aromatic amines, arsenic in drinking water, and exposure to certain drugs (eg, cyclophosphamide) (3, 4). Intakes of various foods and nutrients could also influence the risk of bladder cancer, because most metabolites are excreted through the urinary bladder. With regard to dietary factors, consumption of milk and other dairy foods could potentially reduce the risk of bladder cancer (3). However, results from epidemiologic studies of milk intake and bladder cancer risk have been inconsistent: most studies have reported weak, nonsignificant inverse associations (3), which may reflect small sample sizes. Data from animal studies (5–7) and randomized trials of bladder cancer recurrence (8, 9) have suggested that the intake of cultured milk products containing lactic acid bacteria may play a role in reducing bladder carcinogenesis. Epidemiologic studies on the association of cultured milk or yogurt intake with bladder cancer risk are limited (10–12).

Given the inconsistent findings for milk intake and the paucity of data on cultured milk intake in relation to bladder cancer risk, we investigated the association between the intake of total and specific dairy foods, including cultured milk, and the incidence of bladder cancer in a large, prospective, population-based study of Swedish women and men.

SUBJECTS AND METHODS

Study population

Our study population consisted of participants in the Swedish Mammography Cohort (SMC) and the Cohort of Swedish Men. The SMC was established between 1987 and 1990, when all women born between 1914 and 1948 and residing in central Sweden (Västmanland and Upplands counties) received a mailed questionnaire on diet, body size, and education. In the fall of 1997, all surviving participants received a new expanded questionnaire that included ≈350 items concerning diet and other lifestyle factors, including smoking status and history; 39,227 women (70% response rate) returned a completed questionnaire. The Cohort of Swedish Men was initiated in the fall of 1997, when all men born between 1918 and 1952 and residing in central Sweden (Västmanland and Örebro counties) received a mailed questionnaire that was identical (except for some sex-specific questions) to the SMC 1997 questionnaire; 48,850 men (49% of the total) answered the questionnaire. The cohort represents the Swedish population because the age distribution, relative body

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weight, and educational level are very similar to those of the overall middle-aged and elderly Swedish population (13).

Because the SMC 1987–90 questionnaire did not include data on smoking and because smoking is a strong risk factor for bladder cancer, eligible participants for the present analyses were women and men who completed the 1997 questionnaire. Of those, we excluded participants with an erroneous or missing National Registration Number, those with implausible values for total energy intake (ie, 3 SDs from the log$_e$-transformed mean energy intake in women and men), and those with a previous diagnosis of cancer (except nonmelanoma skin cancer) at baseline. After these exclusions, 82,002 participants (36,664 women and 45,338 men), aged 45–83 y in 1997, remained for analyses.

The subjects’ completion of the self-administered questionnaire was considered to convey written informed consent. The study was approved by the Regional Ethics Committee of the Karolinska Institute (Stockholm, Sweden).

Dietary assessment

Diet was assessed at baseline by using a self-administered food-frequency questionnaire on which participants reported their average frequency of consumption of 96 foods and beverages over the past year. For most of the food items, 8 categories for frequency of consumption were provided, ranging from never to ≥3 times/d. For some commonly consumed foods, such as milk, cultured milk (sour milk and yogurt), and cheese, participants could fill in the exact number of servings per day or week. In a validation study of the food-frequency questionnaire, the corrected Pearson correlation coefficients for dairy foods between that questionnaire and the mean intake assessed by four 1-wk diet records ranged from 0.4 for cheese to 0.7 for cultured milk (A Wolk, unpublished data, 1992).

Ascertainment of bladder cancer cases

Incident bladder cancer cases were identified by computerized record linkage of the study population (using the National Registration Number assigned to each Swedish resident) to the National Swedish Cancer Register and the Regional Cancer Register covering the study area. The completeness of cancer ascertainment of the study population (using the National Registration Number, those with implausible values for total energy intake (ie, 3 SDs from the log$_e$-transformed mean energy intake in women and men), and those with a previous diagnosis of cancer (except nonmelanoma skin cancer) at baseline. After these exclusions, 82,002 participants (36,664 women and 45,338 men), aged 45–83 y in 1997, remained for analyses.

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RESULTS

During a mean follow-up of 9.4 y (772,272 person-years), 485 participants (76 women and 409 men) were diagnosed with bladder cancer. Baseline characteristics of the study cohort by total dairy intake are shown in Table 1. Compared with women and men with a low intake of dairy foods, those with higher intakes had slightly lower alcohol intake, but they consumed more coffee, cultured milk, and fruit and vegetables. Other characteristics did not vary appreciably across categories of dairy intake. We found no statistically significant association between total dairy intake and risk of bladder cancer (Table 2). Among individual dairy foods, a statistically significant inverse association was observed only for cultured milk intake. The multivariate RR of bladder cancer for participants in the highest category of cultured milk intake (≥2 servings/d) compared with those who never consumed cultured milk was 0.62 (95% CI: 0.46, 0.85; P for trend = 0.006). The association was similar among women (RR = 0.55; 95% CI: 0.25, 1.22; P for trend = 0.06) and men (RR = 0.64; 95% CI: 0.46, 0.89; P for trend = 0.03). The age- and sex-standardized incidence rates of bladder cancer per 100,000 person-years of follow-up were 46.3 in participants who consumed ≥2 servings of cultured milk per day and 75.8 in those who never consumed cultured milk. The multivariate RR of bladder cancer for a 1-serving/d increment in the consumption of cultured milk was 0.87 (95% CI: 0.77, 0.99). Intake of cheese or milk was not significantly related to bladder cancer risk (Table 2).
The association between dairy food intake and bladder cancer did not vary materially by stage or grade of disease. The multivariate RRs comparing the highest with the lowest category of cultured milk intake were 0.63 (95% CI: 0.43, 0.94) for superficial bladder cancer and 0.64 (95% CI: 0.30, 1.36) for invasive and advanced bladder cancer. The RRs for lower-grade and high-grade disease were 0.77 (95% CI: 0.44, 1.36) and 0.56 (95% CI: 0.36, 0.89), respectively. We found no statistically significant modifying effect by smoking status. The multivariate RRs of bladder cancer for the highest compared with the lowest category did not vary materially by stage or grade of disease. The multivariate RRs comparing the highest with the lowest category of milk were 0.77 (95% CI: 0.44, 1.36) and 0.56 (95% CI: 0.30, 1.36) for invasive and advanced bladder cancer. The RRs for lower and higher-grade disease were 0.84 (95% CI: 0.50, 1.39) and 0.36 (95% CI: 0.18, 0.70), respectively. We found no statistically significant modifying effect by smoking status. The study found no statistically significant modifying effect by smoking status. The multivariate RRs of bladder cancer for the highest compared with the lowest category of cultured milk intake were 0.53 (95% CI: 0.36, 0.79) among nonsmokers and 0.72 (95% CI: 0.44, 1.19) among smokers.

**DISCUSSION**

In this large prospective study of Swedish women and men, a high intake of cultured milk was associated with a significantly lower risk of bladder cancer. Women and men who consumed ≥2 servings of cultured milk per day had a 38% lower risk of bladder cancer compared to those who never consumed cultured milk. No association was observed for the intake of total dairy, cheese, or milk.

Few studies have examined the relationship between the consumption of cultured milk or yogurt and bladder cancer risk. As is consistent with our results, a population-based case-control study in Japan found that consumption of fermented milk products containing lactic acid bacteria was associated with a significantly lower risk of bladder cancer (10). Another case-control study reported a statistically significant inverse relation between yogurt consumption and bladder cancer (11). No statistically significant relation between yogurt consumption and bladder cancer incidence or mortality was observed in a cohort study of Japanese men and women (12, 16). Cultured milk products contain lactic acid bacteria, which have been shown to suppress bladder carcinogenesis in rodents (5–7). Furthermore, in a double-blind randomized trial, intake of the lactic acid bacterium *Lactobacillus casei* strain Shirota significantly decreased the recurrence of superficial bladder cancer after transurethral resection (8, 9). The mechanism accounting for the antitumor effect of lactic acid bacteria is not clear, but it may be related to modulation of the immune system (5). In addition, oral administration of lactic acid bacteria has been shown to suppress food-derived urinary mutagenicity in humans (17), thus possibly reducing bladder carcinogenesis.

Epidemiologic studies of milk consumption in relation to the risk of bladder cancer are inconsistent. Among 15 case-control studies, 8 showed a lower risk of bladder cancer with high milk consumption (10, 11, 18–23), and this difference was statistically significant in 5 of the studies (11, 18, 20, 22, 23); 4 other case-control studies reported a nonsignificant positive association (24–27), and 3 studies stated that there was no significant association (28–30). Inverse associations between milk consumption and bladder cancer incidence were observed in 4 prospective cohort studies (12, 31–33), but the associations were not statistically significant. A Japanese cohort study found that men and women who consumed milk almost every day had a significantly (53%) lower risk of death due to bladder cancer than did those who consumed <2 servings milk/mo (16).

The current study has several strengths, including its population-based and prospective design, a large sample size (the largest to date in a study of dairy foods and bladder cancer risk), detailed data on diet and smoking history, and the completeness of case ascertainment through linkage to Swedish cancer registries. The prospective design precludes recall bias, and
the nearly complete follow-up minimized the likelihood that our results were affected by bias due to differential follow-up of exposed and unexposed participants. Because of the observational design of the present study, we cannot entirely rule out the possibility that our findings are due to confounding from other uncontrolled risk factors. We cannot exclude measurement error due to self-reported diet as a contributor to the lack of relations for total dairy, cheese, and milk intake in the present study. However, we observed inverse associations of dairy, cheese, and milk intake with colorectal cancer risk in this study population (34, 35), and it is therefore unlikely that our failure to observe a protective association was due to an inability to assess the intake of these foods.

In summary, findings from this prospective study suggest that a high intake of cultured milk may reduce the risk of developing bladder cancer. Our data, however, do not provide support for a protective association between the intake of cheese or milk and bladder cancer risk. The association between cultured milk intake and the risk of bladder cancer merits further investigation.

The authors’ contributions were as follows—SCL and AW: study concept and design; AW: data collection; SCL: statistical analyses and writing of the manuscript; and SCL, S-OA, J-EJ, and AW: interpretation of results and critical revision of manuscript. None of the authors had a personal or financial conflict of interest.

REFERENCES

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<th>Category of intake</th>
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<th>2</th>
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<td>&lt;3.5 (2.6)</td>
<td>3.5–4.9 (4.3)</td>
<td>5.0–6.9 (5.9)</td>
<td>≥7.0 (8.9)</td>
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<td>102</td>
<td>101</td>
<td>135</td>
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<tr>
<td>Person-years (n)</td>
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<td>180,396</td>
<td>192,477</td>
<td>184,787</td>
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<tr>
<td>Age- and sex-adjusted RR (95% CI)</td>
<td>1.00</td>
<td>0.81 (0.63, 1.05)</td>
<td>0.68 (0.53, 0.88)</td>
<td>0.94 (0.74, 1.18)</td>
<td>0.62</td>
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<td>Multivariate RR (95% CI)</td>
<td>1.00</td>
<td>0.82 (0.64, 1.06)</td>
<td>0.67 (0.51, 0.88)</td>
<td>0.87 (0.66, 1.15)</td>
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<td>Cheese</td>
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<tr>
<td>Servings/d</td>
<td>&lt;1.5 (1.0)</td>
<td>1.5–2.4 (2.0)</td>
<td>2.5–4.4 (4.0)</td>
<td>≥4.5 (6.0)</td>
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<td>Cases (n)</td>
<td>157</td>
<td>117</td>
<td>137</td>
<td>74</td>
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<td>Person-years (n)</td>
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<td>195,122</td>
<td>223,211</td>
<td>117,650</td>
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<td>1.00</td>
<td>0.83 (0.66, 1.06)</td>
<td>0.81 (0.65, 1.02)</td>
<td>0.89 (0.67, 1.17)</td>
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<td>1.00</td>
<td>0.85 (0.67, 1.08)</td>
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<td>0.78 (0.58, 1.07)</td>
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<td>Servings/d</td>
<td>&lt;0.5 (0.2)</td>
<td>0.5–1.0 (1.0)</td>
<td>1.1–2.0 (1.9)</td>
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<td>128</td>
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<td>Person-years (n)</td>
<td>234,532</td>
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<tr>
<td>Age- and sex-adjusted RR (95% CI)</td>
<td>1.00</td>
<td>0.99 (0.77, 1.26)</td>
<td>0.89 (0.69, 1.15)</td>
<td>0.99 (0.78, 1.27)</td>
<td>0.84</td>
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<tr>
<td>Multivariate RR (95% CI)</td>
<td>1.00</td>
<td>0.99 (0.77, 1.28)</td>
<td>0.90 (0.70, 1.17)</td>
<td>0.97 (0.75, 1.26)</td>
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<td>0.1–0.9 (0.4)</td>
<td>1.0–1.9 (1.0)</td>
<td>≥2.0 (2.0)</td>
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<td>Cases (n)</td>
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<td>111</td>
<td>122</td>
<td>55</td>
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<td>Person-years (n)</td>
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<td>204,929</td>
<td>206,805</td>
<td>119,735</td>
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<tr>
<td>Age- and sex-adjusted RR (95% CI)</td>
<td>1.00</td>
<td>0.87 (0.69, 1.09)</td>
<td>0.89 (0.71, 1.12)</td>
<td>0.61 (0.46, 0.83)</td>
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<tr>
<td>Multivariate RR (95% CI)</td>
<td>1.00</td>
<td>0.90 (0.71, 1.14)</td>
<td>0.95 (0.75, 1.20)</td>
<td>0.62 (0.46, 0.85)</td>
<td>0.006</td>
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</table>

1 RRs and 95% CIs were estimated by using Cox proportional hazards models.
2 Median in parentheses (all such values).
3 Adjusted for age, sex, education, cigarette smoking (smoking status and pack-years of smoking), and total energy intake. Milk, cheese, and cultured milk are included in the same multivariate model.

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