Intake of milk and other dairy products and the risk of bladder cancer

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ARTICLE

Food and health

Intake of milk and other dairy products and the risk of bladder cancer: a pooled analysis of 13 cohort studies

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Abstract

Background Inconsistent associations between milk and other dairy product consumption and bladder cancer (BC) have been reported. We aimed to investigate possible associations with BC risk for total and individual dairy products by bringing together the world's data on this topic.

Methods Thirteen cohort studies, included in the BLadder cancer Epidemiology and Nutritional Determinants (BLEND) study, provided data for 3590 BC cases and 593,637 non-cases. Associations between milk and other dairy product consumption and BC risk were investigated using Cox proportional hazard regression analyses stratified by study center and adjusted for potential confounders.

Results Overall, total 'other' dairy product consumption was not associated with BC risk (HR comparing highest with lowest tertile: 0.97 (95% CI: 0.87–1.07; $p_{trend} = 0.52$) and likewise no association was observed for either liquid milk, processed milk, cream, cheese or icecream. However, an inverse association was observed between yoghurt consumption and BC risk when comparing those in the moderate (25–85 g/day) and high categories (>85 g/day) with non-consumers, with multivariate HR of 0.85 (95% CI: 0.75–0.96) and 0.88 (95% CI: 0.78–0.98), respectively.

Conclusions We found no evidence of association between either total or individual dairy products and BC risk, but suggestive evidence that consumption of yoghurt may be associated with a decreased risk.

Supplementary information The online version of this article (https://doi.org/10.1038/s41430-019-0453-6) contains supplementary material, which is available to authorized users.

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Introduction

Bladder cancer (BC) is the nineth most common cancer worldwide with over 400,000 cases occurring yearly [1]. Globally, the age-adjusted incidence rate per 100,000 is ~9.0 for men and 2.2 for women [2]. The highest incidence has been reported in North America, Southern and Western Europe, Western Asia and the lowest incidence in Western, Middle and Eastern Africa [3]. BC is also the most expensive malignancy to treat from diagnosis to death, with an estimated cost ranging from $96,000 to 187,000 per patient annually in the United States [4, 5]. The European Union spent €4.9 billion in 2012 on BC representing about 5% of the total health care costs [6].

Smoking is the most important risk factor for BC [7]. Other established risk factors include age, sex, bladder infections, occupational exposures and genetic factors [8, 9]. Because the bladder is an excretory organ through which dietary components and metabolites are excreted, diet might also play an essential role in the development of BC [10, 11]. The World Cancer Research Fund/American Institute for Cancer Research report on diet and cancer concludes that there is limited, suggestive evidence that combined intake of fruits and vegetables, tea reduce BC risk, however evidence on all other dietary factors are inconclusive [11] hence the pressing need to identify foods and nutrients associated with BC.

Milk and other dairy products are a rich source of calcium, other nutrients and bioactive constituents [12, 13], which are suggested to play a vital role in promoting human health and preventing diseases. Several epidemiological studies have already investigated the role of milk and other dairy products in the development of BC but their findings have been inconclusive [11]. While most previous studies found no significant associations, some case control [14–19] and cohort studies [20–22] have reported significant inverse associations for BC risk with intake of milk and majorly fermented dairy products. This inverse association has been attributed to their lactic acid bacteria content which may prevent BC carcinogenesis [23, 24]. Many other previous cohort studies have reported inconclusive evidence, but consistent relative risk estimates. Of the meta-analyses investigating the association between dairy foods and BC risk using aggregated data, one showed no overall association between milk or other dairy products and BC [25] while another found a significant inverse association [26] between milk consumption and BC risk.

This inconsistent evidence could be due to the known problems associated with retrospective case-control studies and to the small sample sizes of previous studies and their consequent lack of statistical power to detect weak associations [27]. We aimed to provide a more precise quantitative estimate for the associations between milk and other dairy products and the risk of developing BC by pooling data restricted to those available from cohort studies.

Materials and methods

Study sample

Data were analyzed from the BLadder cancer Epidemiology and Nutritional Determinants (BLEND) study: a large international nutritional consortium, comprising a total of 11,261 cases and 675,532 non-cases aged between 18 and 100 years from different countries in Europe, America, Australia and Asia. Thirteen of the sixteen cohort studies included in the BLEND, comprising a total of 3590 cases and 593,637 non-cases, had sufficient information on food items to be eligible for inclusion in our study on the intake of milk and other dairy products and risk of developing BC. Studies originated from USA[4], Sweden[1], the Netherlands[1,2], Australia[1,3], Denmark[1], France[1], Germany[1], Greece[1], Italy[1], Spain[1] and the UK[1]. The participating cohort studies were the European Prospective Investigation into Cancer (1), The Netherlands Cohort Study (2), The Melbourne Collaborative Cohort Study (3) and the VITamins And Lifestyle study (4).

Data collection and coding

Details of the methodology of the BLEND consortium have been described elsewhere [27]. Briefly, the primary data from all included studies were incorporated into one dataset. All data were checked and converted from daily, monthly or yearly food intake to weekly intake. National specific standard portions sizes for each food item were used to calculate intake in grams per day. Dietary data from all studies were recorded using the hierarchical Eurocode 2 food coding system version 99/2 [28]. In addition to information on dietary intake, the BLEND data also included study characteristics (design, method of dietary assessment, recall time of dietary intake and geographical region), participant demographics (age, sex and ethnicity) and smoking status (current/former/never). Both the dietary data and study characteristics were all measured at baseline.

Dairy food assessment

Food frequency questionnaires were used to collect information on consumption of milk and/or other dairy products in all studies. All data were checked and converted from weekly to daily consumption. Milk was assessed separately as liquid milk (<1%, 2–2.9, 3–4, >4% fat) and processed milk (chocolate flavoured milk, fruit flavoured, evaporated milk, dried milk, condensed milk, filled milk, butter milk, acidophilus milk and whey). "Total 'other' dairy products" is a sum variable for all the other individual dairy products, which included cheese (fresh, soft, hard, semi-hard, blue cheese, smoked, processed and whey cheese), ice cream (dairy ice cream), cream (<15 to >50% fat) and yoghurt (<1 to >3% fat).

Statistical analysis

To assess the association between milk and other dairy products and BC risk, Cox proportional hazard regression analysis, stratified by study center, was used to obtain hazard ratios and corresponding 95% confidence intervals. Person-years at risk were calculated from baseline, using age at inclusion within the cohort as starting point for the time scale until diagnosis of BC, death, loss to follow-up or end of the follow-up, whichever occurred first. The proportional hazards assumption was examined through scaled Schoenfeld residuals [29]. To further examine a possible violation of the assumption, -ln (-ln (survivor function)) as a function of time on the logarithmic scale plots were generated and graphically assessed [30].

We undertook separate analyses for each dairy product, as well as for total 'other' dairy products consumption combined. All milk and dairy products were firstly compared ever (individuals whose intake is over 0 per day) versus never intake. Analyses for milk were done per cup of milk (1, 2, 3, >3 cups/day) consumed per day, with one cup equivalent to 250 ml. Dairy product consumption was expressed as tertiles of users, based on the distribution of the participants included in the analysis; non-consumers served as the reference group. We analyzed males and females combined in both crude (model 1) and multivariate adjusted models. Adjustments were made for the predefined confounders age, sex and smoking status (model 2) and additionally for the following potential confounders: total intake of fruits (grams/day), vegetables (grams/day), meat (grams/day), beverages (milliliters/day) and energy intake (kcal/day) (model 3). We used the Wald-test to derive the p-value for linear trend by comparing the model with the categorized exposure variable with the model with the same exposure variable as a continuous model. Tests for interaction between milk and other dairy product consumption and sex; and smoking status were performed by introducing cross-product terms into the regression model and the Wald-test was used to test for the presence of interaction. All statistical analyses were performed using STATA version 14 (StataCorp LP, College Station, TX) and a two-sided p-value < 0.05 was considered statistically significant.

Results

Baseline characteristics

Baseline characteristics of the study population are described in Table 1. Altogether, 3590 cases and 593,637 non-cases were included in our analyses. Compared with non-cases, BC cases were older (60.6 years) and more likely to be male (75%). Cases were also mostly current or former smokers (71%). The mean consumption of liquid milk (246 ml/day) was slightly higher for cases while the total consumption of other dairy products (97 g/day) was higher for the non-cases compared with cases (Table 1).

Additional baseline characteristic for the included studies are shown in Supplementary Table 1.

Milk

No evidence of an association was observed between either liquid milk or processed milk consumption and risk of developing BC, neither when comparing ever with non-consumers nor those who consumed up to 1, 2, 3 or >3 cups/day with non-consumers (Table 2).

Other dairy products

No association was observed for total dairy products consumption and BC risk, (adjusted HR comparing highest with lowest tertiles: 0.97, 95% CI:0.87–1.07, p-trend = 0.52). When analyzing the individual dairy products, no association was found for cream, cheese or ice cream (Table 2) while an inverse association was observed only for yoghurt consumption (adjusted HR 0.88, 95% CI: 0.80–0.96) when comparing ever with non-consumers; and similarly, for the comparison of both the moderate (25–85 g/day and median intake 54 g/day) and high (>85 g/day and median intake 130 g/day) categories with the non-consumers, with a multivariable HRs of 0.85 (95% CI: 0.75–0.96) and 0.88 (95% CI: 0.78–0.98, p-trend = 0.02), respectively. Stratified analyses by sex and smoking status revealed similar associations (results not shown).

Discussion

To our knowledge, this is the largest pooled analysis of cohort studies to investigate the association between milk and other dairy products consumption and risk of developing BC.

We observed no association between the consumption of liquid milk, processed milk, cream, cheese or ice cream and BC risk. We observed an inverse association for yoghurt consumption and BC risk but no dose-response trend with

Table 1 Baseline characteristics and dairy food consumption among non-cases and Bladder Cancer cases in the BLEND Study

Categories of data	Non-cases	Cases
Cohort studies [13]	593,637	3590
Age years (mean (SD))	52.83 (10.20)	60.61 (7.32)
Gender (%)		
Male	195,700 (33.0)	2701 (75.2)
Female	397,937 (67.0)	889 (24.8)
Smoking status (%)		
Current	121,385 (20.4)	1021 (28.5)
Former	175,439 (29.6)	1530 (42.6)
Never	296,813 (50.0)	1039 (28.9)
Continent (%)		
Europe [12]	517,583 (87.2)	3212 (89.5)
America [1]	76,054 (12.8)	378 (10.5)
Milk and dairy products		
Liquid milk, ml/day (mean (SD)) [13]	218.68 (214.69)	246.29 (238.82)
Processed milk, ml/day (mean (SD)) [2]	201.05 (269.92)	64.96 (104.69)
Total dairy products, g/day (mean (SD)) [13]	425.96 (371.21)	302.57 (348.39)
Cream, g/day (mean (SD)) [13]	3.67 (5.91)	5.02 (11.23)
Yoghurt, g/day (mean (SD)) [12]	76.99 (88.83)	70.99 (79.42)
Cheese, g/day (mean (SD)) [13]	35.33 (34.13)	31.28 (29.82)
Ices, g/day (mean (SD)) [12]	10.32 (15.10)	11.95 (18.39)
Potential confounders		
Fruits, g/day (mean (SD))	122.18 (115.24)	124.13 (115.30)
Vegetables, g/day (mean (SD))	199.38 (145.69)	208.93 (142.53)
Beverages, ml/day (mean (SD))	1253.66 (873.30)	1430.49 (892.06)
Meat, g/day (mean (SD))	74.12 (56.46)	84.08 (55.30)
Energy intake, kJ/day (mean (SD)	2067.07 (711.45)	2234.36 (735.89)

increasing intake, suggesting no causal association. People who consumed >25 g/day of yoghurt had a reduction of up to 15% in the risk of developing BC compared with non-consumers.

Milk and other dairy products are a rich source of many nutrients which have been shown to have protective associations with several malignancies including colorectal, breast and BC [12, 31, 32]. The main dairy components with potential anticancer properties include calcium, vitamin A and vitamin D [13, 19]. The protective mechanisms of calcium and vitamin D have been linked to their role in the reduction of cell proliferation and their ability to induce apoptosis [13], however a recent randomized placebo-control trial for vitamin D has shown no lower incidence of cancer associated with its intake [33]. Vitamin A has been linked to suppressed malignant transformation in vitro [34] as well as its antioxidant properties, and therefore ability to neutralize free radicals preventing them from causing cell damage [35].

In line with our findings, Li et al. [25] in a meta-analysis of six cohort studies, showed no overall association between total 'other' dairy product consumption and BC risk (RR 0.95; 95% CI: 0.71–1.27). In addition, the NIH-AARP Diet and Health Study conducted in the US by Park et al. [12], also found no association between total dairy foods consumption and BC risk in both men and women, however a decreased risk was observed in men (p-trend = 0.03) with higher intake of dairy foods.

Several observational studies on the consumption of fermented dairy products or yoghurt have shown a decreased risk of BC associated with their consumption. A Spanish case-control study showed a protective effect for yoghurt consumption (OR 0.34, 95% CI: 0.12–0.97) and BC risk among both men and women combined [15]. Another case-control study on fermented milk consumption, conducted by Ohashi et al. [16], also showed a decrease in BC risk for those that consumed fermented milk in the previous 10–15 years, (OR 0.46, 95% CI: 0.27–0.79) for 1–2 times/week and (OR 0.61, 95% CI: 0.38–0.99) for 3–4 or more times/week compared with those who consumed ≤1–2 times/month. A Swedish cohort study also reported decreased risk with consumption of >2 servings/day of cultured milk in both men and women combined (RR 0.62, 95% CI:0.46–0.85) in women and men combined [21]. In a

Table 2 Hazard ratios and 95% confidence intervals for bladder cancer in both sexes combined according to consumption of milk and other dairy products in BLEND study

Milk							
Liquid milk							p_{trend}
Cut off points, cup (250 ml)/day	Never consumption	Ever consumption	≤1	≤2	≤3	>3	
No. of cases	326	2063	1252	460	280	71	
Person years	873,633	5,388,262	3,378,020	1,340,935	522,206	147,101	
HR (95% CI)[a]	1	1.06 (0.91–1.22)	1.07 (0.92–1.24)	0.96 (0.80–1.14)	1.16 (0.96–1.40)	1.10 (0.84–1.45)	0.41
HR (95% CI)[b]	1	1.08 (0.93–1.24)	1.09 (0.94–1.26)	1.02 (0.86–1.21)	1.14 (0.95–1.38)	0.93 (0.71–1.22)	0.96
HR (95% CI)[c]	1	1.06 (0.90–1.25)	1.07 (0.90–1.26)	1.00 (0.82–1.23)	1.22 (0.98–1.52)	0.92 (0.66–1.27)	0.57
Processed milk							
Cut off points, cup (250 ml)/day	Never consumption	Ever consumption	≤1	>1			
No. of cases	568	654	632	22			
Person years	363,459	176,388	144,354	32,034			
HR (95% CI)[a]	1	0.98 (0.87–1.11)	1.00 (0.88–1.13)	0.78 (0.51–1.20)			0.57
HR (95% CI)[b]	1	0.97 (0.86–1.09)	0.98 (0.87–1.11)	0.79 (0.51–1.21)			0.44
HR (95% CI)[c]	1	0.96 (0.85–1.09)	0.97 (0.85–1.11)	0.75 (0.44–1.29)			0.41
Dairy products							
Total ‘other’ dairy							
Median intake, g/day	19	75	170				
No. of cases	1359	1041	854				
Person years	1,941,002	2,187,314	2,163,722				
HR (95% CI)[a]	1	0.89 (0.82–0.97)	0.79 (0.72–0.87)				$p < 0.001$
HR (95% CI)[b]	1	0.97 (0.88–1.05)	0.96 (0.87–1.05)				0.36
HR (95% CI)[c]	1	0.95 (0.86–1.04)	0.97 (0.87–1.07)				0.52
Cream							
Cut off points, g/day	Never intake	Ever intake	0–1.2	1.2–3.2	>3.2		
No. of cases	1785	1432	425	499	508		
Person years	2,096,388	4,193,093	1,382,315	1,389,542	1,421,236		
HR (95% CI)[a]	1	0.81 (0.72–0.91)	0.79 (0.69–0.91)	0.79 (0.68–0.91)	0.85 (0.74–0.98)		0.71
HR (95% CI)[b]	1	0.93 (0.83–1.05)	0.92 (0.80–1.06)	0.91 (0.80–1.06)	0.97 (0.84–1.11)		0.71
HR (95% CI)[c]	1	0.98 (0.85–1.14)	0.99 (0.83–1.17)	0.96 (0.82–1.13)	1.00 (0.85–1.18)		0.97
Yoghurt							
Cut off points, g/day	Never intake	Ever intake	0–25	25–85.7	>85.7		
No. of cases	927	1981	787	539	655		
Person years	1,213,568	4,615,794	1,617,310	1,474,341	1,524,143		
HR (95% CI)[a]	1	0.70 (0.64–0.76)	0.79 (0.72–0.88)	0.66 (0.59–0.73)	0.64 (0.58–0.71)		$p < 0.001$
HR (95% CI)[b]	1	0.88 (0.81–0.96)	0.91 (0.82–1.01)	0.87 (0.78–0.97)	0.87 (0.78–0.96)		0.01
HR (95% CI)[c]	1	0.88 (0.80–0.96)	0.90 (0.80–1.00)	0.85 (0.75–0.96)	0.88 (0.78–0.98)		0.02
Cheese							
Cut off points, g/day	Never intake	Ever intake	0–16.6	16.6–38.1	>38.1		
No. of cases	163	3090	1121	1116	853		
Person years	203,269	6,084,161	1,947,233	2,098,094	2,038,834		
HR (95% CI)[a]	1	0.91 (0.77–1.07)	0.90 (0.76–1.07)	0.89 (0.75–1.05)	0.96 (0.81–1.15)		0.63
HR (95% CI)[b]	1	0.98 (0.83–1.15)	0.96 (0.81–1.14)	0.97 (0.82–1.16)	1.04 (0.87–1.24)		0.28
HR (95% CI)[c]	1	0.93 (0.78–1.12)	0.93 (0.77–1.12)	0.92 (0.77–1.11)	0.97 (0.79–1.17)		0.82
Ice cream							
Cut off points, g/day	Never intake	Ever intake	0–3	3–8.6	>8.6		
No. of cases	438	1895	636	633	626		
Person years	1,157,296	5,040,748	1,604,851	1,716,882	1,719,015		
HR (95% CI)[a]	1	0.97 (0.86–1.09)	0.95 (0.83–1.09)	1.00 (0.87–1.16)	0.96 (0.83–1.10)		0.78
HR (95% CI)[b]	1	1.00 (0.89–1.14)	1.02 (0.89–1.17)	1.07 (0.93–1.24)	0.95 (0.82–1.09)		0.37
HR (95% CI)[c]	1	1.02 (0.88–1.18)	1.06 (0.90–1.24)	1.08 (0.92–1.27)	0.93 (0.79–1.10)		0.22

Never consumption: individuals who intake 0 per day

Ever consumption: individuals who intake over 0 per day

HR hazard ratio, *CI* confidence interval

[a]Crude models

[b]Models adjusted for age, sex and cigarette smoking status

[c]Models adjusted for age, sex and cigarette smoking status and additionally, total intake of fruits, vegetables, meat, beverages and energy

double-blind randomized control trial in Japan, a particular *Lactobacillus casei* strain *Shirota* was associated with reduced recurrence of BC after transurethral resection [23, 24]. However, one cohort study found no association between consumption of yoghurt and BC [22]. The protective effect of fermented dairy products on BC might be explained by their component lactic acid bacteria, which has been shown to play a role in modulating the immune response, suppress bladder carcinogenesis in rodents [36], potentially increase antioxidative enzyme activity as well as modulate circulatory oxidative stress [37, 38] thus protecting cells against carcinogen induced damage.

Another emerging possible explanation for the protective effective by yoghurt may be due to its vitamin B2 (riboflavin) content as reported in a recent paper by Bassett et al. [39]. While milk contains high amounts of vitamin B2 too, the fermentation process and presence of bacteria in the yoghurt helps to lower the lactose content of yoghurt compared with milk possibly making it better tolerated and absorbed [40]. As a water-soluble vitamin B2/riboflavin comes into direct contact with the bladder epithelium and when consumed in excess, is excreted via the urine. Fermentation, additionally to lowering lactose content, also increases phenolic compounds that have antioxidative action [41].

Furthermore, in line with our findings, Li et al. [25], also showed in a meta-analysis of 14 cohort and case-control studies, no overall association between milk consumption and BC risk when comparing high versus low consumption levels (RR 0.89; 95% CI: 0.77–1.02). In contrast, however, the most comprehensive meta-analysis to date showed that the overall consumption of milk was significantly associated with a decreased risk of developing BC (OR high versus low, 0.84; 95% CI: 0.71–0.97) [26].

Most of the individual cohort studies have shown inverse associations for milk consumption and BC risk [22, 42–45] with this association being statistically significant only in one [22]. This could be due to the fact that the putative association is weak and previous studies had insufficient statistical power to find the true association [27]. In contrast to most previous cohort studies, the current study uses non-consumers as the reference group.

Our study has some methodological limitations. First, residual confounding may have occurred because we were not able to adjust for the duration and frequency of smoking and other potential confounders such as physical activity, body mass index, occupational exposure, and other dietary factors that may influence BC risk. But there is only limited inconsistent and inconclusive evidence suggesting that such factors may play a role [11]. Second, the use of food frequency questionnaires for dietary assessment by all of the included studies could have led to systematic and random errors when we estimated the total intake of milk and other dairy products [46]. Third, many of the included studies did not report sub-types of milk/dairy products therefore preventing specific analyses for individual sub-types of milk/dairy products. Fourth, all events other than BC were analyzed as censored. This was done because of lack of specific information (i.e. reason) on loss-to-follow-up subject. We were therefore, unable to perform competing risk analyses in addition to the survival analyses. Finally, in view of multiple statistical testing it could be debated whether, for instance, Bonferroni p-value adjustments should have been applied. However, it previously has been argued that the use of Bonferroni p-value adjustments is impractical and likely too conservative when testing a priori hypotheses [47]. Since we were able to formulate plausible a priori hypotheses regarding most of the tested milk products, based on data from previous studies, we did not apply Bonferroni correction in our analyses.

Our study's predominant strengths include: (a) a large sample size allowing for detailed analyses with sufficient power; (b) the use of individual participant data, enabling adjustments to be made for the same confounders across all studies thus eliminating possible sources of heterogeneity; and (c) use of prospective cohort studies only, which precludes recall bias which commonly occur in case-control studies and retrospective cohort studies.

Conclusion

Overall, we found no evidence of association with either liquid milk, processed milk, total 'other' dairy products, cream, cheese or ice cream and BC risk, but suggestive evidence that consumption of yoghurt reduces BC risk.

Further studies should be conducted to establish the biological mechanisms pertaining consumption of fermented dairy products on bladder carcinogenesis.

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Author Contribution Study conception and design: AW and MPZ; analyses and interpretation of data: MA; drafting of the manuscript: MA; revised the manuscript: AW, FVO, EYY and MPZ; provided the data: PAB, EW, HOA, EW, MB, GGG and RLM; approved the manuscript: all the authors.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval Each participating study has been approved by the local ethic committee.

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