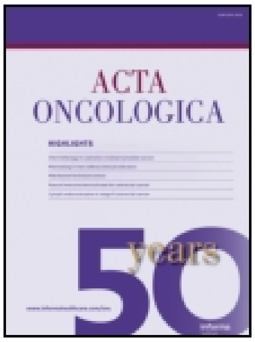

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ORIGINAL ARTICLE

Use of dairy products, lactose, and calcium and risk of ovarian cancer – Results from a Danish case-control study

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Abstract

Background. A number of epidemiological studies have examined the association between use of dairy products and risk of ovarian cancer, but results are conflicting. Using data from a large Danish population-based case-control study we here further examined the association between dairy consumption, lactose, and calcium and risk of overall ovarian cancer and histological types of ovarian cancer. *Material and methods.* In the period 1995–1999 we included 554 women with epithelial ovarian cancer and 1554 randomly selected age-matched controls (35–79 years). All women participated in a detailed personal interview that included questions about dairy consumption. Data were analysed using multiple logistic regression models. *Results.* Total dairy intake was associated with ovarian cancer risk (OR = 1.11; 95% CI: 1.07–1.15 per 100 ml/day). The association was strongest for milk [OR = 1.14; 95% CI: 1.03–1.27 per glass (200 ml)/day], soured milk products [OR = 1.49; 95% CI: 1.22–1.81 per portion (250 ml)/day] and yoghurt [OR = 1.65; 95% CI: 1.22–2.23 per portion (250 ml)/day]. In contrast, intake of cheese was associated with a decreased risk [OR = 0.70; 95% CI: 0.55–0.89 for > 1 portion (100 ml)/day compared with no intake]. Intake of lactose, but not calcium, was also associated with an increased ovarian cancer risk (OR = 1.24; 95% CI: 1.10–1.40 per 10 g of lactose/day). Similar risk patterns were observed for the different histological types of ovarian cancer, indicating virtually identical aetiologies with regard to dairy intake, lactose, and calcium. *Conclusions.* Our results indicate that intake of dairy products is associated with a modest increased risk of ovarian cancer. In addition, ovarian cancer development was associated with lactose intake

Ovarian cancer is the most lethal gynaecologic cancer, with an overall five-year survival of approximately 40% in European countries [1]. The highest incidence and mortality rates occur in Western countries, and Denmark has one of the world's highest incidence (11.0 per 100 000 women) and mortality rates (7.0 per 100 000 women) of ovarian cancer (World Standard Population) [2].

Due to the geographical variation in ovarian cancer incidence it has been suggested that lifestyle parameters, such as type of diet may influence the risk of developing ovarian cancer. In 1989, Cramer [3] first reported that *per capita* milk consumption and lactose tolerance were significantly correlated with national incidence rates of ovarian cancer. Since then, several epidemiological studies have investigated the association between dairy consumption and risk of ovarian cancer, but the results are conflicting [4–19]. Concerning dairy products, seven studies [4,5,11–14,17] found that dairy intake increased ovarian cancer risk, while seven other studies [6–10,15,18] found no evidence of an association. In addition, three studies [13,16,19] found that intake of milk or cheese was inversely related to ovarian cancer risk. A number of epidemiological studies have also examined the influence of specific nutrients from dairy products, including lactose, calcium, and fat, in the development of ovarian cancer [4–14,18,19]. However, these results are also contradicting as four studies [4–6,13] found that lactose intake increases ovarian cancer risk, six studies [7,8,10,11,18,19] found no statistically significant

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association, and one study [9] found a decreased risk of ovarian cancer. Two studies [9,10] found that calcium intake reduces the risk of ovarian cancer, one study [14] found that calcium intake increases the risk, and one study found no evidence of a statistically significant association [6]. Furthermore, some investigators found that ovarian cancer risk increases with intake of dairy products with a high fat content [7,11,12]. Lastly, only few studies have examined the role of dairy intake in relation to risk of specific histological types of ovarian cancer [4,6,7,13], and the results were inconclusive.

Thus, the role of dairy products in ovarian cancer development remains unclear. In the present study, we therefore examined the association between intake of specific dairy products and related nutrients (lactose and calcium) and ovarian cancer risk using data from a large population-based case-control study among Danish women. In addition, we examined whether the association between intake of dairy products and ovarian cancer risk differed by histological types.

Material and methods

The study is based on data from the Danish MALOVA (MALignant OVArian cancer) study, a population-based case-control study on ovarian cancer. The design of the study has been described in detail elsewhere [20].

Cases

Briefly, from January 1995 to May 1999 women aged 35–79 years who were scheduled for an explorative laparotomy or laparoscopy because of suspicion of an ovarian tumour were requested to participate in the study with blood and tissue samples and a personal interview. The women were recruited from 16 gynaecological departments in Denmark. To ensure that all eligible cases in the study area were included the study database was linked to the Danish Cancer Registry every second month. The Danish Cancer Registry contains nationwide information about all incident cases of invasive cancer diagnosed in Denmark since 1943. It is supplemented by linkage to the Causes of Death Registry and the National Patient Registry to ensure complete data [21]. Women with ovarian tumours were allocated to a personal interview, which took place at the hospital immediately or as soon as possible after the diagnosis. The interview included information on social, reproductive, medical, and gynaecological history, family history of cancer and lifestyle factors.

By May 1999, a total of 959 cases of histologically verified malignant ovarian tumours were identified in the study area. Among these, 53 women were considered too ill to participate, and 45 women died before contact was made, leaving 861 women as eligible cases. A total of 180 women did not want to participate leaving 681 women (79.1%) to be included in the MALOVA study; 579 with a personal interview and 102 only with a blood sample. For the present study, women only participating with a blood sample and women with nonepithelial tumours ($n = 25$) were excluded, leaving 554 women with invasive, epithelial ovarian tumours (hereafter denoted ovarian cancer) to be included in the final analyses. Among these, 343 were serous adenocarcinomas, 50 were mucinous adenocarcinomas, 75 were endometrioid adenocarcinomas, and 86 were other types of adenocarcinomas (including undifferentiated and papillary adenocarcinomas, and clear-celled neoplasms).

Controls

Using the unique Danish personal identification number as the key identifier we drew a random sample of women aged 35–79 years from the general female population in the study area. Controls were included simultaneously with cases and frequency matched in five-year intervals using the age distribution of women with ovarian cancer registered in the Danish Cancer Registry from 1987 to 1992. In all, 3839 women were invited as controls with a personal interview and a blood sample. Among these, contact could not be achieved with 301 women, 269 women were excluded due to bilateral oophorectomy, six women had moved out of the study area, and 126 women were too ill to participate, leaving 3137 women as eligible controls. In all, 1021 women refused to participate in the study, and 2116 women (67.5%) were included as controls of whom 1564 participated with a personal interview and 552 participated with a telephone interview. For the present study we only included the 1564 women with a personal interview as the telephone interview was less comprehensive and did not include questions about intake of dairy products.

Assessment of dairy products and nutrients

Dairy consumption was assessed from open-ended questions on intake of the following dairy products: milk (all types), soured milk products (soured milk products other than yoghurt, e.g. junket, buttermilk, and kefir), yoghurt, cheese (all types), and sour cream or double cream in the year before diagnosis for cases and in the year before the interview for controls. Other dairy products, such as ice cream or butter were not addressed. Moreover, the questionnaire did not capture dairy consumption from cooked foods, baked goods, or packaged foods. In addition, both cases and controls were asked about their intake of dairy products in childhood. For each dairy product, the respondent indicated the usual consuming frequency per day, week, month, or year. The serving sizes for each dairy product were pre-specified in the questionnaire as one glass of milk = 200 ml; one portion of soured milk products or yoghurt = 250 ml; one portion of cheese = 100 ml; and one portion of sour cream or double cream = 1 tablespoonful (15 ml). For analyses we calculated the frequency of each dairy product quantity (glasses or portions) consumed per day. In addition, we calculated the frequency of total intake of dairy products per day as the sum of each dairy product multiplied by portion size.

Intake of lactose and calcium from each dairy product was calculated by multiplying the daily consumption frequency for each dairy product by portion size and nutrient content per 100 g. The nutrient content of dairy products was determined from the Danish Food Composition Databank [22]. However, the nutrient content varies with different types of specific dairy products [22], and the MALOVA questionnaire did not contain information on intake of specific types of dairy products. Therefore we based our calculations of lactose and calcium intake on assumptions about consumption of different types of dairy products during the study period. To take into account the variation of lactose and calcium content in specific types of milk and sour cream or double cream we calculated the weighted average of lactose and calcium content based on statistics of per capita consumption of these two products in Denmark for the year 1997 [23,24]. Correspondingly, we calculated the weighted average of lactose and calcium content in cheese by use of information about nationwide production of different types of cheese in Denmark in 1997 [23]. In contrast, for soured milk products and yoghurt no information on per capita consumption or nation-wide production of different types of these products was available. Instead, we used the nutrient content of junket to calculate the total intake of nutrients from soured milk products and the nutrient content of medium fat, plain yoghurt to calculate the total intake of nutrients from yoghurt. Based on these assumptions we calculated the following weighted average nutrient contents for the different dairy products as: one glass of milk (all types) (200 ml): 9.34 g of lactose and 240.43 mg of calcium; one portion of soured milk products (250 ml): 8.43 g of lactose and 492.5 mg of calcium; one portion of yoghurt (250 ml): 6.23 g of lactose and 340 mg of calcium; one portion of sour cream or double cream (15 ml): 0.42 g of lactose and 11.22 mg of calcium; one portion of cheese (100 ml): 0.25 g of lactose and 637.97 mg of calcium. Total intake of lactose and calcium from all dairy products was calculated as the sum of the weighted average nutrient content from each dairy product.

We also intended to investigate the effect of dairy associated fat intake on cancer risk. However, the fat content in specific types of dairy products varies to a much larger degree compared with the lactose and calcium content [22], which impaired meaningful calculations of the fat content in different dairy products.

Data analysis

The association between intake of dairy products in adulthood and ovarian cancer was analysed using multiple logistic regression analysis by estimating odds ratios (OR) and corresponding 95% confidence intervals (CI) for ovarian cancer overall and separately for each histological type (serous, endometrioid, mucinous, and other types of adenocarcinomas). In all analyses we adjusted for age in five-year categories corresponding to the sampling of controls. Furthermore, all analyses were adjusted for pregnancy (ever/never), number of pregnancies (linear), oral contraceptive use (ever/never), duration of oral contraceptive use (linear), hormone replacement therapy use (ever/never), and family history of breast and/or ovarian cancer. These potential confounders were selected based on *a priori* knowledge of their possible causal role in the development of ovarian cancer. We also considered other potential confounders as adjustment variables (educational level, smoking status, age at menarche, BMI, breastfeeding, and age at first and last pregnancy) but these variables did not alter the fit of the model. For the analyses of the effect of dairy nutrients we also calculated total intake of lactose and calcium using either the lowest or the highest content of lactose and calcium for each type of dairy product. Analyses using these measures were compared with analyses using the weighted average of nutrient contents in dairy products. Only minor changes of the estimates were found, and no change in the direction of the association was observed. Two statistical models were fitted to estimate the association between lactose and calcium, respectively, and ovarian cancer risk. Model 1 included adjustment for the selected potential confounders, whereas Model 2 also included mutual adjustment between lactose and calcium intake in addition to adjustment for the selected potential confounders. The mutual adjustment in Model 2 was performed as intake of lactose and calcium was highly correlated (Spearman Correlation Coefficient = 0.677, $p < 0.0001$).

We also examined the influence of dairy consumption in childhood, but the influence of childhood dairy consumption on ovarian cancer risk was similar to the influence of dairy consumption in adulthood. Furthermore, we performed all analyses of adult dairy consumption with adjustment for dairy consumption in childhood, but this adjustment did not alter the results substantially and childhood dairy consumption was not included as a potential confounder in the final model. Finally, all analyses were stratified by menopausal status, but the results for pre- and postmenopausal women did not differ. Hence, all analyses presented in this paper refer to the association between adulthood dairy consumption and risk of ovarian cancer without stratification by menopausal status.

Linearity for all quantitative variables except age was tested by comparison with a model with spline effects with knots placed at the tertiles. No significant deviations from linearity were found for any of the variables. All statistical analyses were performed using the PROC GENMOD procedure in the SAS software package (Version 9.2; SAS Institute, Cary, NC, USA).

Results

The mean age was 58.9 years [standard deviation (S.D.) = 10.7] for cases and 57.1 years (S.D. = 11.3) for controls. Eighty-five percent of cases and 93% of controls had ever been pregnant, and both ever pregnancy (OR = 0.38; 95% CI: 0.28–0.52) and additional number of pregnancies (OR = 0.88; 95% CI: 0.81–0.95) reduced the risk of ovarian cancer. Oral contraceptives were used by 43% of cases and 55% of controls and also reduced ovarian cancer risk (OR = 0.60; 95% CI: 0.47–0.76). Furthermore, a dose-response relation between oral contraceptive use and ovarian cancer was observed, where each extra year of oral contraceptive use decreased the risk of ovarian cancer (OR = 0.95; 95% CI: 0.92–0.97). Other risk factors included ever use of hormonal replacement therapy (OR = 1.26; 95% CI: 1.02–1.55) and a history of breast and/or ovarian cancer in first-degree relatives (OR = 1.45; 95% CI: 1.10–1.90) (data not shown).

Table I presents odds ratios (ORs) for overall ovarian cancer in relation to consumption of different dairy products. Adjustment for the selected potential confounders made virtually no changes to the estimates. We found that consumption of ≥ 500 ml of total dairy products/day was associated with an almost two-fold increased risk of ovarian cancer compared with consumption of < 100 ml of total dairy products/day (OR = 1.90; 95% CI: 1.34–2.71). When the linearity of the association was evaluated using a linear spline, the within-category estimate of the dose-response relation between total dairy products and ovarian cancer risk showed an increased ovarian cancer risk of 11% (95% CI: 1.07–1.15) associated with 100 extra ml of total dairy product/day.

Consumption of all types of milk was associated with an increased ovarian cancer risk of 41% (95% CI: 1.04–1.91) among women who consumed more than two glasses of milk/day compared with women who did not consume milk. Furthermore, we found that each extra glass of milk/day among women who drank milk was associated with an increased risk of 14% (95% CI: 1.03–1.27). For women who consumed more than one portion of soured milk products or yoghurt per day, the ORs of developing ovarian cancer were 1.88 (95% CI: 1.39–2.53) and 2.03 (95% CI: 1.49–2.77), respectively, compared with women who did not consume these dairy products. Among women who consumed soured milk products or yoghurt, one extra portion per day was associated with a risk increase of 49% (95% CI: 1.22–1.81) and 65% (95% CI: 1.22–2.23), respectively. Consumption of sour cream or double cream was associated with an increased risk for each extra portion per day (OR = 1.42; 95% CI: 1.11–1.82). Notably, intake of cheese was associated with a protective effect against ovarian cancer (OR = 0.67; 95% CI: 0.52–0.87 for >0 – <1 portion/day and OR = 0.70; 95% CI: 0.55–0.89 for >1 portion/day compared with no intake of cheese). However, there was no linear association between number of extra portions of cheese per day and ovarian cancer risk.

In Table II ORs for histological types of ovarian cancer in relation to intake of dairy products are presented. In general, the associations resembled those observed for overall ovarian cancer presented in Table I. However, due to a smaller number of cases, the risk estimates for the different histological types, mucinous tumours in particular, were less precise than the risk estimates for overall ovarian cancer, and many estimates were not statistically significant. As serous and endometrioid tumours were the most frequent types, the associations observed for these two types resembled those for overall ovarian cancer the most. We observed virtually similar risk estimates for mucinous, serous, endometrioid, and other ovarian cancer tumours.

Table III presents ORs for the association between total intake of lactose and calcium from dairy products and overall risk of ovarian cancer. The table presents ORs based on two analytic models: Model 1 that includes adjustment for the selected potential confounders and Model 2 that also includes mutual adjustment between lactose and calcium intake. Lactose intake was associated with an increased ovarian cancer risk and adjustment for calcium intake made

Table I. Odds ratios (OR) and 95% confidence intervals (95% CI) for the association between consumption of dairy products and ovarian cancer risk.

Dairy products	Cases (n = 554) n	Controls (n = 1564) n	OR (95% CI)†	OR (95% CI)‡
Total dairy (ml/day)				
< 100*	55	218	1.0	1.0
≥ 100 - < 200	47	194	0.96 (0.62-1.49)	0.91 (0.58-1.43)
≥ 200 - < 300	100	307	1.26 (0.87-1.83)	1.20 (0.82-1.76)
≥ 300 - < 500	131	381	1.33 (0.93-1.90)	1.26 (0.87-1.82)
≥ 500	195	383	1.96 (1.39-2.77)	1.90 (1.34-2.71)
p-value for trend			< 0.0001	< 0.0001
Per 100 ml dairy/day			1.10 (1.06-1.14)	1.11 (1.07-1.15)
All types of milk (glasses/day)				
0	123	379	1.0	1.0
> 0 - ≤ 1	144	437	1.03 (0.78-1.36)	1.09 (0.82-1.46)
> 1 - ≤ 2	148	409	1.14 (0.86-1.50)	1.19 (0.89-1.58)
> 2	125	310	1.29 (0.96-1.73)	1.41 (1.04-1.91)
p-value for trend			0.32	0.15
Per glass milk/day			1.13 (1.02-1.25)	1.14 (1.03-1.27)
Soured milk products (portions/day)				
0	96	358	1.0	1.0
> 0 - ≤ 1	268	811	1.26 (0.97-1.65)	1.29 (0.98-1.70)
> 1	182	356	1.86 (1.39-2.49)	1.88 (1.39-2.53)
p-value for trend			< 0.0001	< 0.0001
Per portion fermented milk product/day			1.46 (1.21-1.77)	1.49 (1.22-1.81)
Yoghurt (portions/day)				
0	172	602	1.0	1.0
> 0 - ≤ 1	270	760	1.25 (1.00-1.56)	1.27 (1.01-1.59)
> 1	103	165	2.07 (1.53-2.80)	2.03 (1.49-2.77)
p-value for trend			< 0.0001	< 0.0001
Per portion yoghurt/day			1.70 (1.28-2.27)	1.65 (1.22-2.23)
Sour cream or double cream (portions/day)				
0	50	116	1.0	1.0
> 0 - ≤ 1	438	1343	0.77 (0.54-1.09)	0.79 (0.55-1.14)
> 1	57	94	1.45 (0.91-2.33)	1.45 (0.89-2.36)
p-value for trend			< 0.01	< 0.01
Per portion sour cream or double cream/day			1.43 (1.12-1.82)	1.42 (1.11-1.82)
Cheese (portions/day)				
0	225	514	1.0	1.0
> 0 - ≤ 1	134	462	0.69 (0.54-0.89)	0.67 (0.52-0.87)
> 1	178	541	0.75 (0.59-0.95)	0.70 (0.55-0.89)
p-value for trend			< 0.01	< 0.01
Per portion cheese/day			1.15 (0.93-1.43)	1.12 (0.90-1.41)

*Only 16 persons did not consume any dairy at all.
†Age-adjusted.
‡Adjusted for age, pregnancy (ever/never), number of pregnancies (linear), oral contraceptive use (ever/never), duration of oral contraceptive use (linear), hormone replacement therapy use (ever/never), and family history of breast and/or ovarian cancer.

virtually no changes to the estimated association (OR = 1.64; 95% CI: 1.17–2.31 for > 15 g/day compared with < 5 g of lactose/day). In addition, 10 g extra lactose/day among women who had an intake of lactose was associated with an increased ovarian cancer risk of 24% (95% CI: 1.10–1.40). Concerning the association between calcium intake and risk of ovarian cancer, we found that mutual adjustment between lactose and calcium intake changed the associations observed in Model 1. Hence, no statistically significant associations between calcium intake and ovarian cancer risk were observed after adjustment for lactose.

In Table IV ORs for the different histological types of ovarian cancer in relation to total intake of lactose and calcium are presented. Due to a smaller number of cases, the risk estimates were less precise than the risk estimates for overall ovarian cancer.

Table II. Odds ratios (OR) and 95% confidence intervals (95% CI) for the association between consumption of dairy products and histological types of ovarian cancer.

	Controls	Mucinous		Serous		Endometrioid		Others	
Dairy products	n	n	OR (95% CI)†	n	OR (95% CI)†	n	OR (95% CI)†	n	OR (95% CI)†
Total dairy (ml/day)									
< 100*	218	5	1.0	37	1.0	8	1.0	5	1.0
≥ 100 - < 200	194	6	1.20 (0.35-4.05)	26	0.75 (0.43-1.30)	9	1.27 (0.48-3.40)	6	1.30 (0.39-4.40)
≥ 200 - < 300	307	10	1.29 (0.43-3.88)	57	1.02 (0.64-1.61)	16	1.36 (0.56-3.27)	17	2.36 (0.85-6.57)
≥ 300 - < 500	381	9	0.96 (0.32-2.94)	91	1.26 (0.82-1.94)	17	1.15 (0.48-2.74)	14	1.56 (0.55-4.44)
≥ 500	383	17	1.75 (0.63-4.86)	118	1.71 (1.13-2.59)	23	1.57 (0.69-3.62)	37	4.04 (1.54-10.6)
p-value for trend			0.64		< 0.01		0.82		< 0.01
Per 100 ml dairy/day			1.11 (1.02-1.21)		1.10 (1.05-1.14)		1.09 (1.01-1.18)		1.13 (1.05-1.21)
All types of milk (glasses/day)									
0	379	8	1.0	84	1.0	11	1.0	20	1.0
> 0 - ≤ 1	437	15	1.74 (0.72-4.17)	92	1.01 (0.72-1.41)	24	2.09 (1.00-4.37)	13	0.59 (0.28-1.23)
> 1 - ≤ 2	409	15	1.78 (0.74-4.29)	84	0.92 (0.65-1.30)	20	1.92 (0.90-4.09)	29	1.69 (0.92-3.13)
> 2	310	11	1.82 (0.72-4.64)	76	1.24 (0.87-1.77)	19	2.56 (1.18-5.54)	19	1.44 (0.73-2.83)
p-value for trend			0.50		0.44		0.08		< 0.05
Per glass milk/day			1.13 (0.86-1.48)		1.13 (1.00-1.28)		1.14 (0.92-1.43)		1.25 (1.01-1.55)
Soured milk products (portions/day)									
0	358	6	1.0	60	1.0	21	1.0	9	1.0
> 0 - ≤ 1	811	30	2.30 (0.94-5.62)	162	1.26 (0.90-1.76)	36	0.80 (0.46-1.40)	40	2.08 (0.99-4.39)
> 1	356	14	2.33 (0.88-6.20)	117	1.96 (1.37-2.80)	18	0.77 (0.40-1.49)	33	3.30 (1.53-7.09)
p-value for trend			0.12		< 0.001		0.68		< 0.01
Per portion fermented milk product/day			1.39 (0.84-2.29)		1.57 (1.25-1.97)		1.12 (0.68-1.84)		1.34 (0.88-2.04)
Yoghurt (portions/day)									
0	602	13	1.0	114	1.0	24	1.0	21	1.0
> 0 - ≤ 1	760	31	1.77 (0.91-3.44)	166	1.16 (0.89-1.53)	32	1.13 (0.65-1.95)	41	1.65 (0.95-2.85)
> 1	165	5	1.34 (0.46-3.84)	59	1.72 (1.19-2.50)	18	2.70 (1.40-5.20)	21	3.46 (1.79-6.69)
p-value for trend			0.22		< 0.05		< 0.05		< 0.01
Per portion yoghurt/day			1.16 (0.54-2.49)		1.56 (1.09-2.24)		1.65 (0.93-2.92)		1.62 (0.92-2.86)
Sour cream or double cream (portions/day)									
0	116	3	1.0	30	1.0	9	1.0	8	1.0
> 0 - ≤ 1	1343	42	1.18 (0.36-3.93)	271	0.83 (0.54-1.29)	58	0.58 (0.28-1.24)	67	0.78 (0.36-1.70)
> 1	94	4	1.95 (0.41-9.15)	37	1.56 (0.88-2.77)	8	1.21 (0.44-3.37)	8	1.27 (0.44-3.66)
p-value for trend			0.65		< 0.05		0.12		0.45
Per portion sour cream or double cream/day			1.25 (0.65-2.40)		1.42 (1.09-1.86)		1.43 (0.89-2.28)		1.21 (0.75-1.96)
Cheese (portions/day)									
0	514	17	1.0	135	1.0	31	1.0	42	1.0
> 0 - ≤ 1	462	12	0.78 (0.37-1.68)	91	0.75 (0.55-1.02)	17	0.64 (0.35-1.18)	14	0.38 (0.20-0.72)
> 1	541	18	0.92 (0.46-1.82)	108	0.72 (0.54-0.96)	26	0.76 (0.44-1.31)	26	0.57 (0.34-0.95)
p-value for trend			0.82		0.06		0.33		< 0.01
Per portion cheese/day			1.10 (0.59-2.05)		1.08 (0.83-1.42)		1.20 (0.71-2.03)		1.32 (0.78-2.24)

*Only 16 persons did not consume any dairy at all.
†Adjusted for age, pregnancy (ever/never), number of pregnancies (linear), oral contraceptive use (ever/never), duration of oral contraceptive use (linear), hormone replacement therapy use (ever/never), and family history of breast and/or ovarian cancer.

The analyses revealed no major differences in the risk estimates for the different histological types. Mutual adjustment between lactose and calcium intake made virtually no changes to the estimated associations between intake of lactose and risk of histological types of ovarian cancer. In contrast, with mutual adjustment between lactose and calcium intake a statistically significant association between calcium intake and risk of any of the histological types of ovarian cancer was no longer present.

Table III. Odds ratios (OR) and 95% confidence intervals (95% CI) for the association between total intake of lactose and calcium from dairy products and ovarian cancer risk.

Nutrient	Cases (n = 554) n	Controls (n = 1564) n	OR (95% CI)*	OR (95% CI)†
Total lactose intake (g/day)				
< 5	103	420	1.0	1.0
≥ 5 - < 10	98	323	1.19 (0.86-1.64)	1.16 (0.84-1.62)
≥ 10 - < 15	107	256	1.70 (1.23-2.36)	1.64 (1.17-2.29)
≥ 15	220	484	1.85 (1.40-2.44)	1.64 (1.17-2.31)
p-value for trend			< 0.0001	< 0.01
Per 10 g lactose/day			1.26 (1.15-1.37)	1.24 (1.10-1.40)
Total calcium intake (mg/day)				
< 400	129	439	1.0	1.0
≥ 400 - < 800	141	470	1.03 (0.77-1.36)	0.90 (0.67-1.20)
≥ 800 - < 1200	125	304	1.34 (1.00-1.81)	1.07 (0.77-1.48)
≥ 1200	133	270	1.59 (1.18-2.14)	1.00 (0.68-1.48)
p-value for trend			< 0.01	0.69
Per 400 mg calcium/day			1.16 (1.07-1.25)	1.02 (0.92-1.13)

*Model 1: Adjusted for age, pregnancy (ever/never), number of pregnancies (linear), oral contraceptive use (ever/never), duration of oral contraceptive use (linear), hormone replacement therapy use (ever/never), and family history of breast and/or ovarian cancer.
†Model 2: Adjusted for all the factors in Model 1 plus mutual adjustment between lactose intake and calcium intake.

Lastly, we investigated whether the risk of ovarian cancer associated with total dairy intake, total milk consumption, and total lactose intake varied according to pregnancy, oral contraceptive use, and family history of breast and/or ovarian cancer, i.e. whether there was a possible interaction between dairy intake and these three potential effect modifiers. However, our results provided no evidence that the risk of ovarian cancer associated with dairy intake was modified by any of these factors (data not shown).

Discussion

Our results showed that intake of dairy products, particularly milk, soured milk products, and yoghurt, was associated with an increased overall ovarian cancer risk. A similar association was found between lactose intake and overall ovarian cancer risk. In contrast, intake of cheese was associated with a decreased risk, while there was no association between intake of calcium and ovarian cancer risk. These findings were also evident for the histological types of ovarian cancer, although they were less strong due to lack of statistical power.

The increased ovarian cancer risk with total intake of dairy products and milk observed in our study is consistent with findings from two recent prospective cohort studies, the Swedish Mammography Cohort Study [4] and the Iowa Women's Health Study [14]. In addition, these two studies, together with the prospective Nurses' Health Study [13], found a higher risk of ovarian cancer risk with increasing consumption of milk. In the Swedish Mammography Cohort Study [4], women who consumed more than one glass of milk (all kinds) per day had a risk of developing serous ovarian cancer twice that of women who never or seldom drank milk. The Nurses' Health Study [13] found that women who consumed one or more glasses of skimmed or semi skimmed milk daily had a 69% higher risk of serous ovarian cancer than women who never or seldom consumed this type of milk. In the Iowa Women's Health Study [14], the association between intake of milk and ovarian cancer risk was confined to skimmed milk. In contrast, other prospective cohort studies [6,7,10] found no evidence of an association, while one prospective cohort study [19] found an inverse association between milk consumption and ovarian cancer risk. Results from previous case-control studies have been inconsistent as two studies report that intake of whole milk is associated with increased ovarian cancer risk, and intake of skimmed or semi skimmed milk is associated with a protective effect [11,12], whereas three other studies found no statistically significant association between milk consumption and ovarian cancer risk [9,15,16]. Finally, a meta-analysis of 21 studies [5] found an increased risk of ovarian cancer with increasing intake of milk.

Three studies [11,13,17] support our finding that intake of yoghurt is associated with an increased risk of ovarian cancer. For example, in the Nurses' Health Study, Fairfield et al. [13] found that women who consumed ≥ 5 servings of yoghurt per week had a 2.4 times higher risk of serous ovarian cancer than women who almost never consumed yoghurt.

Table IV. Odds ratios (OR) and 95% confidence intervals (95% CI) for the association between total consumption of lactose and calcium from dairy products and histological types of ovarian cancer.

	Controls (n = 1564)	Mucinous			Serous			Endometrioid			Others		
Nutrient	n	n	OR (95% CI)*	OR (95% CI)†	n	OR (95% CI)*	OR (95% CI)†	n	OR (95% CI)*	OR (95% CI)†	n	OR (95% CI)*	OR (95% CI)†
Total lactose intake (g/day)													
< 5	420	9	1.0	1.0	68	1.0	1.0	16	1.0	1.0	10	1.0	1.0
≥ 5 - < 10	323	7	1.06 (0.39-2.89)	0.99 (0.36-2.73)	68	1.24 (0.85-1.80)	1.21 (0.82-1.78)	13	0.96 (0.45-2.05)	0.97 (0.45-2.11)	10	1.20 (0.49-2.95)	1.23 (0.50-3.04)
≥ 10 - < 15	256	12	2.15 (0.88-5.22)	1.93 (0.78-4.79)	57	1.33 (0.90-1.98)	1.27 (0.84-1.91)	16	1.63 (0.79-3.36)	1.61 (0.76-3.43)	22	3.53 (1.61-7.74)	3.71 (1.65-8.34)
≥ 15	484	19	1.88 (0.84-4.23)	1.43 (0.55-3.74)	136	1.69 (1.21-2.35)	1.46 (0.97-2.18)	28	1.50 (0.79-2.84)	1.38 (0.63-3.02)	37	3.34 (1.62-6.88)	3.77 (1.60-8.91)
p-value for trend			0.20	0.45		< 0.05	0.33		0.33	0.51		< 0.001	< 0.001
Per 10 g lactose/day			1.28 (1.03-1.58)	1.22 (0.90-1.66)		1.23 (1.11-1.36)	1.18 (1.03-1.37)		1.24 (1.03-1.49)	1.27 (0.97-1.67)		1.34 (1.13-1.60)	1.40 (1.09-1.81)
Total calcium intake (mg/day)													
< 400	439	13	1.0	1.0	74	1.0	1.0	19	1.0	1.0	23	1.0	1.0
≥ 400 - < 800	470	13	0.89 (0.40-1.95)	0.79 (0.35-1.77)	85	1.06 (0.75-1.50)	0.97 (0.67-1.39)	23	1.17 (0.62-2.20)	1.04 (0.54-2.01)	20	0.88 (0.47-1.65)	0.69 (0.36-1.32)
≥ 800 - < 1200	304	4	0.43 (0.14-1.34)	0.35 (0.11-1.14)	95	1.79 (1.27-2.54)	1.53 (1.05-2.24)	12	0.88 (0.42-1.86)	0.71 (0.32-1.59)	14	0.84 (0.41-1.70)	0.56 (0.26-1.19)
≥ 1200	270	17	1.88 (0.89-3.97)	1.24 (0.47-3.32)	75	1.58 (1.09-2.27)	1.13 (0.71-1.81)	19	1.49 (0.77-2.91)	0.92 (0.38-2.24)	22	1.41 (0.76-2.63)	0.61 (0.26-1.42)
p-value for trend			< 0.05	0.10		< 0.01	< 0.05		0.51	0.77		0.44	0.46
Per 400 mg calcium/day			1.20 (0.99-1.46)	1.06 (0.80-1.41)		1.16 (1.06-1.27)	1.05 (0.92-1.19)		1.13 (0.95-1.34)	0.97 (0.75-1.24)		1.17 (1.00-1.38)	0.95 (0.74-1.20)

*Model 1: Adjusted for age, pregnancy (ever/never), number of pregnancies (linear), oral contraceptive use (ever/never), duration of oral contraceptive use (linear), hormone replacement therapy use (ever/never), and family history of breast and/or ovarian cancer.

†Model 2: Adjusted for all the factors in Model 1 plus mutual adjustment between lactose intake and calcium intake.

However, most studies found no evidence of an association between yoghurt consumption and ovarian cancer risk [6–8,12,18]. One prospective cohort study [7] examined the relation between intake of soured milk products and ovarian cancer and found no statistically significant association. Only one previous case-control study [11] investigated the relation between consumption of cream and development of ovarian cancer, but in contrast to our study no statistically significant increased risk was found. Most studies [6,7,10–12,15,19] found no evidence of an association between intake of cheese and ovarian cancer risk but in agreement with our findings, one case-control study [16] and one prospective cohort study [13] reported that intake of cheese decreased the risk of ovarian cancer. These results suggest that cheese, in contrast to other dairy products, may have a protective effect on development of ovarian cancer, but further studies are needed to clarify this association.

Lactose has been suggested as the causal factor for the association between dairy consumption and ovarian cancer [17]. Using data from a case-control study, Cramer et al. [17] first reported that cases had a significantly higher consumption of lactose than controls. Moreover, they found that the activity of the enzyme galactose-1-phosphate uridyltransferase (GALT), which is involved in the metabolism of galactose, was significantly lower among cases [17]. Furthermore, experimental studies have suggested that the metabolites of lactose (galactose) have a direct toxic effect on the ovaries [25] or that they disturb the normal gonadotropin secretory function [26], which may eventually induce ovarian neoplasia. In agreement with our results, four studies [4–6,13] found that increasing lactose intake was associated with an increased risk of ovarian cancer. In contrast to our results, one case-control study [9] reported an inverse association between total intake of lactose and ovarian cancer risk. Finally, two case-control studies [11,18], three cohort studies [7,10,19], and one meta-analysis [8] did not find evidence of an association between lactose intake and development of ovarian cancer.

Previous results are conflicting with regard to the association between calcium intake and ovarian cancer risk [6,9,10,14]. In accordance with our results one study [6] found no evidence of an association between calcium intake and ovarian cancer. In contrast, one prospective cohort study [14] found that calcium intake increased ovarian cancer risk, while one case-control study [9] and one prospective cohort study [10] found an inverse association with ovarian cancer. There is a possibility that high intake of calcium increases cellular proliferation and carcinogenesis through depression of vitamin D metabolism [27]. In contrast, high intake of calcium may also protect against carcinogenesis by downregulating parathyroid hormone, which is known to act as a co-mitogen and anti-apoptotic factor [28]. The conflicting findings of epidemiological studies in relation to calcium intake and ovarian cancer may reflect these different mechanisms, and further studies are needed to fully clarify the association. In general, effects of nutrients commonly found in the same dairy products are difficult to separate. However, by mutual adjustment between lactose and calcium intake we found evidence of a statistically significant association between lactose intake and ovarian cancer risk, but not between calcium intake and ovarian cancer risk. Therefore, our findings indicate that primarily lactose accounts for the association between intake of dairy products and ovarian cancer risk.

In general, we observed virtually similar risk estimates for mucinous, serous, endometrioid, and other ovarian cancer tumours. Only few studies [4,6,7,13] have examined the association between intake of dairy products, lactose, and calcium according to histological type of ovarian cancer. One prospective cohort study [7] found no statistically significant association between lactose intake and serous ovarian cancer. In contrast, two prospective cohort studies [4,13] found that intake of milk and lactose increased the risk of serous ovarian tumours, but not nonserous ovarian tumours. Only one study by Genkinger et al. [6] analysed the potential differences between several histological types, and in agreement with our study they found that intake of milk and lactose was similarly associated with mucinous, serous, and endometrioid ovarian tumours. Based on these sparse findings there are thus no major indications of differences in the risk profile between histological types of ovarian cancer and intake of dairy products. However, most studies including the present are limited by a relatively low number of cases of some of the histological types, which leads to low statistical power, and further studies addressing differences between dairy consumption and histological types of ovarian cancer are needed.

The strengths of this study include the population-based design, the relatively high number of cases compared with some other case-control studies, reasonably high participation rates among cases and controls, the ability to control for known risk factors for ovarian cancer, and the ability to examine specific histological types of ovarian cancer. However, the study also has some limitations that should be considered. An important limitation is the retrospective nature of the study and the possible introduction of recall bias, which is a source of error in all case-control studies. Additionally, some degree of selection bias cannot entirely be excluded, as the women who did not participate in the study may have differed from the participants. As the MALOVA questionnaire was not designed to obtain information on specific types of dairy products our calculations of nutrient intake from different types of dairy products were based on well-defined assumptions that included information from valid sources (the Danish Food Composition Databank, the Danish Dairy Board, and the Danish Veterinary and Food Administration [22–24]). The effect of lactose and calcium intake from food sources other than dairy products is limited as lactose is found naturally only in dairy products and dairy products are the main source of calcium. However, our findings do not include the effect of secondary intake of lactose and calcium from dairy products used for instance in cooking or from packaged foods. Moreover, intake of calcium from calcium supplementation was not taken into account. Another limitation is the lack of data on dairy fat because it is known to increase the risk of ovarian cancer through increased levels of oestrogen [29]. Consequently, the generalisability of our findings is limited to the use of dairy nutrients considered in this study. Furthermore, it is possible that the observed associations between dairy intake and ovarian cancer reflect characteristics of the women having an intake of dairy products rather than a direct carcinogenic effect of dairy products. Women, who consume dairy products, e.g. drink milk and eat yoghurt, may be different in terms of socioeconomic status, health seeking behavior, etc. from women who do not consume dairy products. We cannot rule out the possibility that the observed increased risk of ovarian cancer associated with dairy products may be due to some unmeasured confounding. Lastly, ovarian cancer may develop over several decades. Accordingly, the association between dairy intake and ovarian cancer found in this study is based on the assumption that dairy intake was constant over time.

In conclusion, the results of this case-control study suggest that frequent intake of most types of dairy products and increasing intake of lactose is associated with a modest increased risk of ovarian cancer. However, results from the existing literature on the association between intake of dairy products and ovarian cancer are conflicting, probably reflecting differences in measurement of exposure and in study design, and further well-designed studies are needed to clarify this relation. Furthermore, the potential harmful effects of dairy products on ovarian cancer risk should be balanced against possible health benefits of dairy consumption, such as reduced risk of low bone mass and stroke.

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