Milk and lactose intakes and ovarian cancer risk in the Swedish Mammography Cohort1–3

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ABSTRACT
Background: High intakes of dairy products and of the milk sugar lactose have been hypothesized to increase ovarian cancer risk, but prospective data are scarce.
Objective: We examined the association between intakes of dairy products and lactose and the risk of total epithelial ovarian cancer and its subtypes.
Design: This was a prospective population-based cohort study of 61 084 women aged 38–76 y who were enrolled in the Swedish Mammography Cohort. Diet was assessed in 1987–1990 with the use of a self-administered food-frequency questionnaire. During an average follow-up of 13.5 y, 266 women were diagnosed with invasive epithelial ovarian cancer; 125 of those women had serous ovarian cancer.
Results: After adjustment for potential confounders, women who consumed ≥4 servings of total dairy products/d had a risk of serous ovarian cancer (rate ratio: 2.0; 95% CI: 1.1, 3.7; P for trend = 0.06) twice that of women who consumed <2 servings/d. No significant association was found for other subtypes of ovarian cancer. Milk was the dairy product with the strongest positive association with serous ovarian cancer (rate ratio comparing consuming ≥2 glasses milk/d with consuming milk never or seldom: 2.0; 95% CI: 1.1, 3.7; P for trend = 0.04). We observed a positive association between lactose intake and serous ovarian cancer risk (P for trend = 0.006).
Conclusions: Our data indicate that high intakes of lactose and dairy products, particularly milk, are associated with an increased risk of serous ovarian cancer but not of other subtypes of ovarian cancer. Future studies should consider ovarian cancer subtypes separately.


KEY WORDS Ovarian cancer, milk, lactose, galactose, diet, epidemiology, cohort studies

INTRODUCTION
The strong correlation between national per capita milk consumption in the United States and the national incidence and mortality rates of ovarian cancer raised the hypothesis that consumption of milk and other dairy products may increase the risk of this malignancy (1–3). Analytic epidemiologic studies investigating this hypothesis have, however, yielded conflicting results. Frequent consumption of whole milk (4–6), yogurt (7), and cheese (7) has been associated with an increased risk of ovarian cancer in some case-control studies. In contrast, evidence suggests a decreased risk of ovarian cancer associated with higher consumption of skim or low-fat milk (4–6, 8, 9). To date, only 2 prospective cohort studies have examined the possibility of an association of the consumption of milk and other dairy products with the incidence of ovarian cancer. In the Iowa Women’s Health Study, women who reported a high consumption of total dairy products, skim milk, and cheese had a higher risk of ovarian cancer than did those who rarely consumed these foods (10). The Nurses’ Health Study found a positive association between consumption of skim or low-fat milk and yogurt and the risk of ovarian cancer, and the findings further suggested that the association might be confined to serous ovarian cancer (11).

Dairy products are the major source of galactose, a component sugar of lactose that may increase ovarian cancer risk by direct toxicity to oocytes or by elevating gonadotropin concentrations, thereby stimulating proliferation of ovarian epithelium (12). A positive association between lactose intake and the risk of ovarian cancer was observed in the Iowa Women’s Health Study (10) and in the Nurses’ Health Study (11), but not in any of 7 case-control studies (5, 8, 13–17).

Given the paucity of prospective data on the intakes of dairy products and of lactose in relation to the incidence of total epithelial ovarian cancer and especially ovarian cancer subtypes, we examined this topic in a large, population-based, prospective cohort study in Sweden. That country has one of the highest rates of ovarian cancer in the world (18), and it citizens consume a wide range of dairy products.

SUBJECTS AND METHODS

Study population
The design of the Swedish Mammography Cohort has been described in detail elsewhere (19). In brief, the cohort was established between 1987 and 1990, when 66 651 women aged 38–76 y and residing in Uppsala and Västmanland counties in

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central Sweden agreed to participate in a mammography screening program and completed a questionnaire that elicited information on weight, height, education level, diet, parity, age at first delivery, and family history of breast cancer. In 1997, a follow-up questionnaire was sent to all surviving cohort members; this questionnaire solicited information on age at menarche, age at menopause, and history of oral contraceptive and postmenopausal hormone use (response rate: 70%). Such data had previously been obtained only from women in Uppsala County at their mammography examination.

For the present analysis, we excluded women with implausibly high or low total energy intake estimates (ie, 3 SD below or above the mean value for log-transformed energy) and women who had a previously diagnosed cancer (except nonmelanomatous skin cancer). In addition, by linkage with the Swedish Inpatient Register, we identified and excluded all women who, before baseline, had undergone a bilateral oophorectomy or a hysterectomy with removal of an unknown number of ovaries. After these exclusions, a total of 61,084 women remained for the analysis. The study was approved by the ethics committees of Uppsala University Hospital and the Karolinska Institutet (Stockholm); their response to the questionnaire constituted the participants’ informed consent.

Dietary assessment

A food-frequency questionnaire with 67 food items was sent to women in 1987–1990 to assess usual dietary intake during the past 6 mo. Women chose from 8 possible response categories that ranged from “never/seldom” to “≥4 times/d.” The questionnaire included 8 specific dairy products: low-fat, medium-fat, and whole milk; low-fat (≤1.5% fat) and regular (3% fat) yogurt; cheese; ice cream; and butter. To calculate nutrients, we used age-specific (<53, 53–65, and >65 y) portion sizes based on mean values from 5922 d of weighed food records among 213 women. We estimated nutrient intakes by multiplying the consumption frequency of each food by portion size and nutrient content (/100 g) and by using composition values from the Swedish National Food Administration Database (20).

The validity of the dietary questionnaire was evaluated in a random sample of 129 women from the cohort by comparing the questionnaire with data from four 1-wk dietary records collected 3–4 mo apart. Pearson’s correlation coefficients ranged from 0.4 to 0.6 for individual dairy products.

Identification of ovarian cancer cases and follow-up of the cohort

Incident ovarian cancer cases that occurred in the cohort from March 1987 through June 2003 were identified by linkage of the study population with 2 independent sources: the national Swedish Cancer Registry and the Regional Cancer Registry covering the study area. The Swedish Cancer Register system covers ≥98% of all newly diagnosed cancers in Sweden (21). We ascertained dates of deaths and dates when a participant moved out from the study area by matching the cohort with the Swedish Death Registry and the Swedish Population Registry.

Statistical analysis

We calculated the follow-up time for each participant from the entry to the cohort (ie, the date of mammography examination) to the date of ovarian cancer diagnosis, the date of a bilateral oophorectomy or a hysterectomy with an unknown number of ovaries removed, the date of death from any cause, the date of migration out of the study area, or 30 June 2003, whichever occurred first. Women were grouped into categories of intake of dairy products and lactose; for each category, we computed the ovarian cancer incidence rate by dividing the number of cases of ovarian cancer by the person-time of follow-up. We used Cox proportional hazards models to estimate hazard rate ratios (RRs), defined as the incidence rate in a particular exposure category divided by the incidence rate in the lowest category. Multivariate models were controlled for age, body mass index (in kg/m²), education level, parity, oral contraceptive use, and intakes of fruit, vegetables, and total energy. Because further adjustment for family history of breast cancer, reproductive factors, and postmenopausal hormone use did not appreciably alter the results, we did not include those data in the final multivariate model. Information on oral contraceptive use was available for 76% of the women in the cohort. Thus, oral contraceptive use was coded as ever, never, and missing. Exclusions of women with missing data for oral contraceptives did not essentially change the results; therefore all analyses are based on all women. Nutrient intake was adjusted for total energy intake by the residual approach (22). We conducted tests for linear trend across categories by modeling the median values of each category as a continuous variable. All reported P values are from two-sided tests.

RESULTS

During 823,572 person-years of follow-up (61,084 women over an average 13.5-y period), we identified 266 incident cases of invasive epithelial ovarian cancer, including 125 serous, 48 endometrioid, 21 mucinous, 5 clear cell, and 67 other or unknown histologic subtypes. The average age at ovarian cancer diagnosis was 64.0 y. The median consumption of total dairy products in the highest consumption categories was 3 times that in the lowest consumption categories. Women who reported a higher consumption of dairy products were more likely to have an education level of ≥12 y, less likely to have a history of oral contraceptive use, and more likely to have a slightly lower body mass index (Table 1). Intakes of total energy, fruit, and vegetables increased across the categories of dairy product consumption.

The multivariate RRs of invasive epithelial ovarian cancer, both overall and by its subtypes (serous and nonserous tumors), according to intakes of dairy products and lactose, are shown in Table 2. Because results of the age-adjusted analyses did not differ substantially from those based on the full multivariate model, we present only the multivariate RRs. Overall, after control for established and potential risk factors, women who consumed ≥4 servings of dairy products/d had a significantly (P for trend = 0.02) greater risk (RR: 1.6; 95% CI: 1.1, 2.5) of ovarian cancer than did women who consumed <2 servings/d (Table 2). Further adjustment for intakes of dietary fat, folate, vitamin C, vitamin E, alcohol, meat, and fish did not materially alter the results (data not shown). The apparent increase in ovarian cancer risk associated with higher dairy product consumption was strong for tumors of the serous subtype and weak, if present at all, for other tumors. In an analysis of cancers of the endometrioid, mucinous, and clear cell subtypes combined (n = 74 cases), the multivariate RRs (adjusted for the same variables as in Table 2)
TABLE 1
Baseline characteristics of 61,084 women in the Swedish Mammography Cohort according to category of total dairy product consumption

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Categories of total dairy product consumption</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>P²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at baseline (y)</td>
<td>53.6 ± 9.7 ±</td>
<td>53.8 ± 9.7</td>
<td>53.9 ± 9.8</td>
<td>53.4 ± 9.8</td>
<td>0.20</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.9 ± 4.0</td>
<td>24.7 ± 3.9</td>
<td>24.6 ± 3.8</td>
<td>24.6 ± 3.8</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Education ≥12 y (%)</td>
<td>10</td>
<td>11</td>
<td>12</td>
<td>13</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Ever had children (%)</td>
<td>88.3</td>
<td>89.2</td>
<td>89.2</td>
<td>89.9</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Ever taken oral contraceptives (%)</td>
<td>56</td>
<td>54</td>
<td>53</td>
<td>53</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Ever taken postmenopausal hormones (%)</td>
<td>53</td>
<td>53</td>
<td>54</td>
<td>53</td>
<td>0.22</td>
<td></td>
</tr>
</tbody>
</table>

Dietary intake

TABLE 2
Invasive epithelial ovarian cancer according to consumption of dairy products

<table>
<thead>
<tr>
<th>Intake</th>
<th>All invasive epithelial tumors</th>
<th>Serous epithelial tumors</th>
<th>Other epithelial tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of cases</td>
<td>RR (95% CI)</td>
<td>No. of cases</td>
</tr>
<tr>
<td>Total dairy (servings/d)³</td>
<td>61</td>
<td>1.0</td>
<td>24</td>
</tr>
<tr>
<td>&lt;2</td>
<td></td>
<td>71</td>
<td>1.2 (0.9,1.7)</td>
</tr>
<tr>
<td>2 to &lt;3</td>
<td></td>
<td>65</td>
<td>1.4 (0.9,2.0)</td>
</tr>
<tr>
<td>3 to &lt;4</td>
<td></td>
<td>69</td>
<td>1.6 (1.1,2.5)</td>
</tr>
<tr>
<td>≥4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P for trend⁴</td>
<td></td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Total milk (servings/d)²</td>
<td>55</td>
<td>1.0</td>
<td>18</td>
</tr>
<tr>
<td>Never or seldom (≤1 serving wk)</td>
<td>54</td>
<td>1.2 (0.9,1.8)</td>
<td>22</td>
</tr>
<tr>
<td>≤1</td>
<td></td>
<td>86</td>
<td>1.2 (0.9,1.8)</td>
</tr>
<tr>
<td>1.1 to &lt;2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥2</td>
<td></td>
<td>71</td>
<td>1.3 (0.9,1.9)</td>
</tr>
<tr>
<td>P for trend⁴</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total yogurt (servings/d)⁵</td>
<td>118</td>
<td>1.0</td>
<td>48</td>
</tr>
<tr>
<td>Never or seldom (&lt;1 serving wk)</td>
<td>66</td>
<td>1.0 (0.7,1.3)</td>
<td>36</td>
</tr>
<tr>
<td>&lt;1</td>
<td></td>
<td>82</td>
<td>1.1 (0.8,1.5)</td>
</tr>
<tr>
<td>P for trend⁴</td>
<td></td>
<td>0.42</td>
<td></td>
</tr>
<tr>
<td>Cheese (servings/d)⁶</td>
<td>81</td>
<td>1.0</td>
<td>36</td>
</tr>
<tr>
<td>&lt;1</td>
<td></td>
<td>107</td>
<td>0.9 (0.7,1.3)</td>
</tr>
<tr>
<td>1 to &lt;2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥2</td>
<td></td>
<td>78</td>
<td>1.2 (0.9,1.7)</td>
</tr>
<tr>
<td>P for trend⁴</td>
<td></td>
<td>0.17</td>
<td></td>
</tr>
</tbody>
</table>

1 Multivariate rate ratios (RRs) were adjusted for age (in 5-y categories), BMI (kg/m²; in quartiles), education level (ie, less than high school, high school, and college), parity (ie, nulliparous, 1–2, and ≥3 children), oral contraceptive use (ever or never), and quartiles of fruit, vegetable, and total energy intakes.

2 Includes 48 endometrioid tumors, 21 mucinous tumors, 5 clear cell tumors, and 67 undifferentiated tumors or tumors of unknown histologic subtypes.

3 Total dairy products included total milk (low-fat, medium-fat, and whole milk), total yogurt (low-fat and regular yogurt), cheese, and ice cream.

4 Two-sided P values for trend were calculated with the Wald statistic by using the median values for each category.

5 Total milk, total yogurt, and cheese were mutually adjusted.

For increasing categories of dairy product consumption were 1.0 (reference), 1.0 (95% CI: 0.5, 2.0), 1.2 (95% CI: 0.6, 2.5), and 1.2 (95% CI: 0.6, 2.6; P for trend = 0.55).

Among the individual dairy products consumed, milk showed the strongest positive association with serous ovarian cancer risk. In analyses of milk modeled in continuous form, each increment of 1 glass of daily consumption of total milk, low-fat milk, and whole milk corresponded to serous ovarian cancer RRs of 1.2 (95% CI: 1.0, 1.4), 1.2 (95% CI: 1.0, 1.6), and 1.3 (95% CI: 0.9, 1.7), respectively. At baseline (entry into the cohort between 1987 and 1990), ≈7% of the study population never or seldom consumed milk. Yogurt consumption showed a modest but
nonsignificant positive relation with the risk of serous ovarian cancer ($P$ for trend = 0.11). By contrast, cheese, ice cream, and butter were not associated with the risk of ovarian cancer overall or of its subtypes. The results were virtually identical when the individual dairy products were included in the model separately, ie, without mutual adjustment (data not shown).

Lactose intake showed a linear positive association with the risk of serous ovarian cancer ($P$ for trend = 0.006; Figure 1). The average lactose intake in the cohort was 12.2 ± 7.8 g/d; milk was the major source. Relative to women with a lactose intake of ≥15 g/d (corresponding to the amount of lactose in 1–2 glasses of milk), those with an intake of <2.5 g/d (the amount of lactose in 50 g milk, ie, 3–4 tablespoons, corresponding to the amount usually added to 1–2 cups of coffee or tea) were less than half (0.4; 95% CI: 0.1, 0.9) as likely to develop serous ovarian cancer. When lactose was analyzed as a continuous variable, each 10 g/d increase in lactose intake (the amount of lactose in ≈1 glass milk) was associated with a 20% greater risk of serous ovarian cancer (multivariate RR: 1.2; 95% CI: 1.0, 1.5). The corresponding RRs for total ovarian cancer and nonserous tumors was 1.1 (95% CI: 0.9, 1.3) and 1.0 (95% CI: 0.8, 1.2), respectively.

When we included intakes of lactose and milk simultaneously in the multivariate model (Pearson’s correlation coefficient: $r = 0.65$), the observed positive association between total milk consumption and the risk of serous ovarian cancer was mostly confined to lactose intake because the relative risk for each 1 glass/d increment in total milk consumption decreased from 1.2 (95% CI: 1.0, 1.4) to 1.0 (95% CI: 0.8, 1.3), whereas the relative risk for increments of lactose intake was essentially unaltered (RR for each 10 g/d increment: 1.2; 95% CI: 0.9, 1.6).

**DISCUSSION**

In this large, population-based, prospective cohort study of Swedish women, intakes of lactose and dairy products, particularly milk, were significantly positively associated with the risk of serous ovarian cancer. Women who consumed ≥1 glass of milk/d had double the risk of serous ovarian cancer compared with women who never or seldom drank milk.

The results of our cohort study are broadly consistent with findings from the Iowa Women’s Health Study (10) and the Nurses’ Health Study (11). In the Iowa Women’s Health Study, in which 139 cases of epithelial ovarian cancer were diagnosed among postmenopausal women, Kushi et al (10) found that women who drank >1 glass of skim milk/d had a 73% greater risk of total ovarian cancer than did those who drank <1 glass of skim milk/wk. They further observed a nonsignificant (60%) increase in the risk of total ovarian cancer when the top (25.2 g/d) and the bottom (<7.7 g/d) quartiles of lactose intake were compared; the associations with specific subtypes of ovarian cancer were not examined. In the report of Fairfield et al (11) from the Nurses’ Health Study, which included 301 cases of epithelial ovarian cancer, those authors documented a 69% greater risk of serous ovarian cancer in women who consumed ≥1 glasses of skim or low-fat milk/d than in women who almost never drank milk. Moreover, women who consumed ≥5 servings of yogurt/wk had a risk of serous ovarian cancer 2.4 times that of women who almost never consumed yogurt. For each 11-g increment in daily lactose intake, the risk of serous ovarian cancer increased by 20%; there was no association with other ovarian cancer subtypes (11).

Five case-control studies to date have related total consumption of dairy products to the risk of ovarian cancer (5, 8, 23–25); none of those studies showed any significant association. Findings for the association of individual dairy products with ovarian cancer risk have been conflicting: there have been reports of no association for any dairy product (15, 16, 26); of positive associations for whole milk (4–6), yogurt (7), and cottage cheese (7); and of inverse associations for total milk (27), skim or low-fat milk (4–6, 8, 9), and cheese (28). The association between lactose intake and ovarian cancer risk has been considered in many case-control studies (5, 7, 8, 13–17). However, only 1 (7) of these 8 studies provided evidence of a positive association between lactose intake and ovarian cancer risk, and that association was restricted to women with low activity of galactose-1-phosphate uridylyltransferase, an enzyme involved in the galactose (a component sugar of lactose) metabolic pathway.

One possible explanation for the discrepancy between cohort studies and case-control studies with respect to the association between consumption of dairy products and ovarian cancer risk may have to do with the retrospective design of the latter type of studies. In the case-control studies, recall bias might have been introduced by overestimation of consumption of skim or low-fat milk and underestimation of consumption of whole milk by controls, which would lead to a spurious inverse association with low-fat milk consumption and a positive association with whole milk consumption. Recall bias, however, is unlikely to explain the absence of association in all case-control studies. Alternatively, a lack of association in some previous studies might be due to the fact that specific ovarian cancer subtypes were not studied. In the present study and in the Nurses’ Health Study (11), the associations with dairy products (milk and yogurt) and lactose intake were restricted to the serous subtype.

We can only speculate about possible mechanisms for the observed increased risk of ovarian cancer associated with high intakes of dairy products (milk and yogurt) and lactose. Milk and yogurt were the major sources of lactose in our study population, contributing approximately two-thirds of total lactose intake. Harlow et al (12) hypothesized that galactose—a component sugar of the disaccharide lactose—might increase the risk of...
ovarian cancer either by direct toxicity to the oocytes or by inducing high concentrations of gonadotropins, thereby stimulating the proliferation of the ovarian surface epithelium. Excess gonadotropin stimulation of the ovaries has been reported in galactosemic women deficient in the galactose-1-phosphate uridylyltransferase enzyme. Ovaries have an unusually high local concentration and a high tissue-specific activity of galactose-1-phosphate uridylyltransferase (29), traits that potentially make them more susceptible to galactose toxicity.

The major strengths of our study include its population-based design, the relatively large number of cases of this cancer, the ability to examine specific subtypes of ovarian cancer, and the completeness of case ascertainment through the Swedish Cancer Register system. Furthermore, in contrast to most studies on the relation between diet and ovarian cancer, our study was based on prospectively collected data, which eliminated bias attributable to differential recall of food intake by women with and without cancer. Moreover, our dietary assessments were based on a validated food-frequency questionnaire that ranked consumption of dairy products well. Our study is limited by its observational character; hence, we cannot exclude the possibility that uncontrolled confounding of our risk estimates by factors that are unmeasured or not accounted for influenced our results. However, adjustment for potential dietary and lifestyle confounding factors did not appreciably alter the results, which suggests that residual confounding is unlikely to explain our observed findings.

In conclusion, this prospective cohort study provides evidence that high intakes of lactose and dairy products, especially milk, may increase the risk of serous ovarian cancer. Continued research is warranted to further elucidate the association and mechanisms for the observed increased risk, and particular focus should be placed on ovarian cancer subtypes.

The contributions of the authors to the manuscript were as follows: study concept and design (SCL and AW), data collection (LB and AW), statistical analyses (SCL), writing the manuscript (SCL), interpreting the results (SCL, LB, and AW), and critical revision of manuscript (LB and AW). All authors reviewed the final manuscript. None of the authors had any financial or personal conflicts of interest.

REFERENCES