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Dairy food and nutrient intake in different life periods in relation to risk of ovarian cancer

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Abstract

Purpose—High lactose intake has been suggested to increase epithelial ovarian cancer (EOC) risk. We evaluated the association between lactose consumed during specific life periods (high school, premenopause, postmenopause) and later risk of EOC.

Methods—We assessed the association of dairy food and nutrient intake with risk of EOC during 28 years of follow-up including 764 cases in the Nurses' Health Study (NHS) and NHSII. Cox proportional hazards regression was used to model the Hazard Ratios (HRs) and 95% confidence intervals (CI) for EOC across categories of dairy food or nutrient intake. We examined dietary intake in adulthood overall, as well as during premenopausal/postmenopausal years and high school.

Results—In analyses of the highest versus lowest cumulative average intake in adulthood, we observed a non-significant inverse association with skim milk intake (HR = 0.76, 95% CI 0.54–1.06, $P_{\text{trend}} = 0.05$), a non-significant inverse association with lactose intake (HR = 0.87, 95% CI 0.69–1.11, $P_{\text{trend}} = 0.22$) and no association with consumption of whole milk, dairy calcium or dairy fat. Similar risk estimates were observed for dairy food/nutrient intake during high school,

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Conflict of interest

The authors declare that they have no conflict of interest.

premenopause or postmenopause. Lactose intake in adulthood was inversely associated with risk of endometrioid EOC (HR = 0.32, 95% CI 0.16–0.65, $P_{\text{trend}} < 0.001$).

Conclusions—These findings do not support the hypothesis that higher lactose intake increases EOC risk. The inverse association with endometrioid tumors deserves further study.

Keywords

ovarian cancer; dairy; milk; lactose; calcium; fat

Introduction

Differences in epithelial ovarian cancer (EOC) incidence rates worldwide [1] suggest that lifestyle factors such as diet may influence the risk for this disease. It has been hypothesized that lactose and its metabolite, galactose, may increase EOC risk through its effects on the ovary/ovarian-pituitary axis [2] by potentially causing toxicity to the oocytes and/or stimulating gonadotropin secretion. Consistent with this hypothesis are animal studies, which observed that mice or rats that were fed high lactose diets developed ovulatory dysfunction and hypogonadism [3,4].

Epidemiologic evidence from cohort studies supports the potential positive association between lactose intake and EOC risk. A pooled analysis of 12 prospective cohort studies (2,132 EOC cases), including the Nurses' Health Study (NHS) and NHSII, reported a modest increased risk of EOC for participants who consumed ≥ 30 g/day of lactose versus <10 (relative risk [RR] = 1.19, 95% confidence interval [CI] = 1.01–1.40, $P_{\text{trend}} = 0.19$) [5]; however, this analysis was limited by the use of only a baseline diet assessment, which prevented the examination of long-term consumption or changes in intake over time. In contrast, most case-control studies have reported no association between lactose intake and EOC risk [6].

In an earlier analysis of the NHS that included follow-up through 1996, we observed a non-significant 40% increased risk in the highest category of lactose intake for invasive EOC and an elevated risk for serous invasive tumors with high lactose intake (Quintile 5 [Q5] versus Q1, RR = 2.07, 95% CI = 1.27–3.40, $P_{\text{trend}} = 0.003$), although the latter finding was based on a small number of cases ($N = 174$) [7]. We and others have observed differences in reproductive risk factors by histologic subtype [e.g., see 8,9,10] and other studies suggest that dietary factors also may exhibit different associations by histologic subtype [11].

A previous study of folate intake in relation to colorectal cancer risk reported that dietary intake at specific time periods had different associations with colorectal cancer risk [12] and similar studies of red meat and breast cancer risk suggest that only adolescent and premenopausal intake are associated with risk [13–16]; thus we hypothesized that inconsistencies in the association between lactose intake and EOC risk could also reflect differences in risk associations with dietary intake at specific time periods throughout life. In the NHS and NHSII we have repeated measurements of diet every 2–4 years during adulthood as well as an assessment of high school diet. Therefore in the current study we evaluated consumption of dairy nutrients (lactose as well as dairy calcium and dairy fat) and

milk intake throughout the life cycle (e.g., during high school, premenopause, postmenopause) in relation to risk of EOC.

Subjects and Methods

The NHS cohort was established in 1976 among 121,701 married, female registered nurses from 11 US states, ages 30 to 55 years. The NHSII began in 1989 among 116,430 female registered nurses, ages 25 to 42 years. All participants completed an initial questionnaire about their lifestyle factors, health behaviors and medical history and since baseline have been followed biennially by questionnaire to update information on risk factors and newly diagnosed diseases [17,18]. Diet was first assessed in the NHS in 1980 using a 61-item semi-quantitative food frequency questionnaire (FFQ). This FFQ was expanded to include 126 items in 1984 and participants completed the expanded FFQ in 1986, 1990 and every four years thereafter until 2006 to update information on diet. Of the 92,468 NHS participants who completed the 1980 FFQ, follow-up through June 2008 was 93% of the potential person-years. In the NHSII, diet was assessed using the 126 item FFQ beginning in 1991 and was updated every four years until 2007. Of the 95,452 NHSII participants who completed the 1991 FFQ, follow-up through June 2009 was 87% of the potential person-years.

Informed consent was provided by all participants, and the study design, data collection, and analyses were performed in accordance with the ethical standards of the institutional review board at the Brigham and Women's Hospital.

Diet in adulthood

The reproducibility and validity of the FFQ have been previously demonstrated [19,20]. For dairy food intake, the FFQ has been found to provide valid estimates of skim/low fat milk and whole milk intake with correlation coefficients between the FFQ and 1-week diet records of 0.81 and 0.62, respectively [21]. Most dairy foods (skim/low fat or whole milk, yogurt, cottage/ricotta cheese, hard cheese, ice cream and butter) were assessed beginning with the 1980 FFQ (NHS) or 1991 (NHSII) until the end of follow-up. Exceptions were sour cream and cream cheese; these were evaluated beginning in 1984 until 2006 in the NHS, and in the NHSII, sour cream intake was assessed only in 1991. The assessment of dairy food intake categories in the FFQ and their corresponding serving size has been previously detailed [7] and similar categories of intake were evaluated in the current study. Dairy nutrient intake (lactose, dairy calcium, dairy fat) was calculated by multiplying the frequency of intake of each dairy food containing the nutrient by the nutrient content of specified portions as determined by the food composition values available from the U.S. Department of Agriculture food composition data [22]. In the NHS in 2002, the primary dietary sources of lactose were skim/low fat milk (63%) and yogurt (15%).

Diet in high school

The details of the NHS and NHSII high school diet FFQs have been described previously [23,24]. Briefly, in 1986, NHS participants were queried about their diet while in high school using a 24-item FFQ which included several dairy products (milk [skim/whole],

milkshakes, ice cream, hard cheese). In 1998, a subset of NHSII women (N = 45,947) completed an extensive 124-item, high school FFQ that was similar to the FFQ used for adult dietary assessment. Assessment of milk intake in high school differed between the NHS and NHSII questionnaires; the NHSII participants were queried about their intakes of milk and chocolate milk separately. The combined estimate for milk intake was calculated by using similar exposure definitions based on reported servings/day (for the NHSII milk intake was the sum of plain milk and chocolate milk). Nutrient intakes were calculated as described for diet in adulthood but using the U.S. Department of Agriculture handbooks and bulletins for foods consumed during the periods that the participants were in high school. Combined estimates for quintiles of intake are based on the distribution of intake in both cohorts.

The reproducibility of recall of the high school diet has been evaluated in both cohorts. In the NHS, a random sample of 275 women were asked in 1994 to again report their high school diet and the average of Spearman correlations between the two recalls of high school diet was $r = 0.57$ overall, with correlations of 0.45 and 0.71 for skim and whole milk intakes, respectively, and $r = 0.62$ for calcium intake [24]. In the NHSII, a similar reproducibility study was carried out in 2002 among 333 randomly selected participants. The mean Spearman rank correlations for milk and all dairy foods were 0.76 and 0.64, respectively, while an intraclass correlation of 0.73 was reported for calcium intake between the first and second diet recalls [23]. In both studies, the correlations between the two recalls of high school diet was substantially higher than the correlation between the first recall of high school diet and their previous current adult diet, suggesting that the reproducibility results were not substantially influenced by current diet. Since a true validation study using data collected during high school from the participants who returned the recalled high school FFQ is not possible, the correlations between 272 NHSII participants and their high school diets as reported by their mothers was assessed [23]. Moderate correlations were found for most nutrients with a Pearson correlation of 0.47 reported for calcium. Together these findings suggest that the high school FFQ provides a reasonable record of the adolescent diet.

Ascertainment of other covariates

We assessed the exposure status for known or suspected risk factors for ovarian cancer based on the participant's responses to the biennial questionnaires. We requested information on parity (defined as pregnancies lasting at least six months), oral contraceptive use, history of tubal ligation, oophorectomy, hysterectomy, menopausal status, age at menopause, postmenopausal hormone use, weight, smoking status, and family history of breast/ovarian cancer on multiple questionnaires during follow-up. In our analysis, we updated values for these covariates when new data were available or otherwise carried forward values from the previous questionnaire cycle.

Documentation of ovarian cancer cases and deaths

We collected information about new EOC diagnoses on each questionnaire. For all reported cases and/or deaths due to EOC identified by family members, the National Death Index, or the U.S. Postal Service, we obtained medical records to confirm the ovarian cancer

diagnosis or linked to a state or SEER cancer registry. A gynecologic pathologist who was blinded to the participant's exposure status reviewed the medical records to confirm the diagnosis and abstract the tumor stage, histologic subtype and invasiveness (borderline or invasive). Tumor grade is not commonly reported and it was not available for the NHS/NHSII cases. In a subset of 215 EOC cases, we previously compared the histological subtype recorded in the pathology report with a standardized review of pathology slides by the gynecologic pathologist and found a concordance of 98% and 83% for tumor invasiveness and histologic subtype, respectively [25]. The medical record review or registry data was used to classify all cases.

Statistical methods

The eligible population for this analysis included 92,468 NHS participants and 95,452 NHSII participants who responded to the 1980 and 1991 FFQs, respectively. Excluded from this analysis at the study baseline were women with a diagnosis of cancer (except nonmelanoma skin cancer) (NHS = 5,221; NHSII = 2,360), bilateral oophorectomy (NHS = 10,489; NHSII = 4,368), menopause due to pelvic irradiation (NHS = 72; NHSII = 60) or who were missing a date of birth (NHS = 46; NHSII = 197). Women who were diagnosed with ovarian cancer (confirmed and unconfirmed cases) (NHS = 29; NHSII = 3) or who died (NHS = 368; NHSII = 108) prior to the study baseline (1984 [NHS] or 1995 [NHSII] when the second FFQ was completed in each cohort) also were excluded. As only participants who had satisfactorily completed the FFQs were included in this study, none of the participants had an extreme caloric intake (<500 or >3500 kcal/day). After these exclusions, a total of 76,243 NHS and 88,356 NHSII participants remained in the analyses.

To investigate the long-term dietary intake of the participants, the main analyses focused on the cumulative average dietary intake from all available dietary questionnaires, representing the overall intake in adulthood. In these analyses each participant accrued person-time beginning with the return of the 1984 (NHS) or 1995 (NHSII) questionnaire until the date of EOC diagnosis, diagnosis of cancer (except nonmelanoma skin cancer), bilateral oophorectomy, pelvic irradiation, death or the end of follow-up (NHS: June 1, 2008; NHSII: June 1, 2009), whichever occurred first. Since the most recent dietary intake could be influenced by disease status, all analyses of the cumulative average dietary intake included a 2–6 year time lag between the diet assessment and the start of the follow-up interval. For example, in the NHS the incidence of EOC from 1984–86 was related to the dietary information from the 1980 questionnaire, the incidence of EOC from 1986–88 was related to the dietary information from the 1984 questionnaire (i.e., the average of 1980 and 1984 FFQs), the incidence of EOC from 1988–90 was related to the dietary information from the 1986 questionnaire (i.e., the average of 1980, 1984 and 1986 FFQs) and so on.

For analyses of dietary intake in high school, we began the follow-up of each variable from the time it was collected; for example, information about high school diet in the NHS was collected in the 1986 questionnaire, and its analysis included person-time beginning in 1986. We also analyzed premenopausal/postmenopausal dietary intake separately by calculating the cumulative average diet until menopause (premenopausal diet) or the cumulative average diet occurring from the time of menopause and thereafter (postmenopausal diet). To evaluate

the latency between the consumption of dairy nutrients or milk and later risk of EOC, analyses were performed using varying lag times (0–4 years, 4–8, 8–12, 12–16) as previously described [12,26]. For example, in the NHS for a latency of 0–4 years, we used the diet reported in 1980 for cases diagnosed from 1980–84, the simple updated diet (i.e., the single dietary measurement) reported in 1984 for cases diagnosed from 1984–86, the simple updated diet reported in 1986 for cases diagnosed from 1986–90 and so on. For a latency of 4–8 years, we used the diet reported in 1980 for cases diagnosed from 1984–88, the simple updated diet reported in 1984 for cases diagnosed from 1988–90, the simple updated diet reported in 1986 for cases diagnosed from 1990–94 and so on.

To control for total energy intake, all nutrient intakes were adjusted for total energy using the residual method [27] and participants were divided into quintiles according to their levels of nutrient intake. Cox proportional hazards regression, with age in months and the 2-year questionnaire cycle as the time scale, was used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations with dairy nutrients and milk, using women in the lowest category of intake as the reference group. All multivariable analyses were adjusted for total caloric intake (continuous), duration of oral contraceptive use (never use, use <1yr [ref], 1–<5 yrs, 5 yrs), parity (adjusting for both parous [yes/no] and the total number of children [continuous]), tubal ligation (yes, no), menopausal status (premenopausal/perimenopausal, postmenopausal) and family history of ovarian cancer in a first degree relative (yes, no). Additional potential confounders (e.g., total fat or caffeine intake, body mass index, history of breastfeeding, use of postmenopausal hormones, smoking status, history of infertility) were evaluated but were not included in the final models because they did not substantially alter the relative risk estimates. To calculate the *P*-value for the test of linear trend, participants were assigned the median value of each nutrient or milk intake category based on the combined NHS/NHSII and this variable was modeled as a continuous term to calculate Wald's statistic. To test for heterogeneity between cohorts, analyses were conducted separately for both cohorts and were then pooled using a random effects model [28]. We did not observe significant heterogeneity between the cohorts, therefore all subsequent analyses were carried out in the pooled NHS/NHSII cohorts using regression models that were stratified by the study time period (2-year questionnaire cycles), age (months) and cohort (NHS, NHSII). Stratified analyses were conducted by menopausal status (postmenopausal, premenopausal/perimenopausal), parity (parous, nulliparous) and oral contraceptive use (ever, never) and a *P*-value for interaction was calculated using a likelihood ratio test to compare models with and without multiplicative interaction terms.

Cox proportional hazards competing risks analysis [29] was used to simultaneously estimate separate HRs and 95% CIs between rapidly fatal (death from ovarian cancer within 3 years of diagnosis) versus less aggressive invasive EOCs [30] and between invasive histologic subtypes of tumors (serous/poorly differentiated [N = 403] versus endometrioid [N = 101]); clear cell and mucinous subtypes were too rare to evaluate. In the competing risks analyses, the likelihood ratio test was used to calculate a *P*-value for heterogeneity comparing a model allowing the association of interest to vary between the two outcome categories to a model

holding the association with the exposure of interest constant across the outcome categories. Analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA).

Results

The study population included 764 incident EOC cases (invasive and borderline malignancies) in the NHS/NHSII cohorts. The majority of cases ($N = 609$) were from the NHS and the distribution of the major histologic subtypes was 58% serous/poorly differentiated invasive, 7% serous borderline, 13% endometrioid, 8% mucinous, 4% clear cell and 11% other. Of the 155 cases from the NHSII, the histologic subtype distribution was 32% serous/poorly differentiated invasive, 9% serous borderline, 17% endometrioid, 13% mucinous, 12% clear cell and 17% other. At the mid-point of each follow-up period in the NHS and NHSII, women with higher lactose consumption also had higher intakes of dairy calcium and dairy fat (Table 1). In the NHSII, women with higher lactose intake were less likely to have had a tubal ligation.

Evaluation of the cumulative average intake of dairy nutrients and milk in adulthood showed non-significant inverse associations (comparing the top versus the bottom quintile) with intake of lactose (HR = 0.87, 95% CI 0.69–1.11, $P_{\text{trend}} = 0.22$) and skim milk (HR = 0.76, 95% CI 0.54–1.06, $P_{\text{trend}} = 0.05$) and no association with consumption of dairy calcium, dairy fat, whole milk or total milk and EOC risk overall (Table 2). We observed similar results after stratifying by menopausal status, oral contraceptive use and parity. There was no association between EOC risk and the cumulative average intake of other dairy foods (yogurt, cottage/ricotta cheese, hard cheese, ice cream, sour cream and cream cheese) (data not shown). These analyses included a 2–6 year time lag between the dietary assessment and the start of the follow-up interval to account for potential changes in dietary intake due to subclinical disease. We observed similar results (e.g., lactose Q5 versus Q1, HR = 0.81, 95% CI: 0.64–1.02, $P_{\text{trend}} = 0.12$) when no time lag was instituted (e.g., diet in 1980 was related to follow-up in 1980–1984 and so on) (data not shown).

We observed differences in the risk associations between serous/poorly differentiated versus endometrioid invasive EOC for the consumption of lactose, total milk and skim milk (P_{het} heterogeneity [P_{het}] = 0.002 for lactose, $P_{\text{het}} = 0.01$ for total milk and $P_{\text{het}} = 0.05$ for skim/low fat milk) (Table 3). High intakes of lactose or milk (total milk or skim/low fat milk) were inversely associated with risk for endometrioid EOC (lactose, Q5 versus Q1, HR = 0.32, 95% CI: 0.16–0.65, $P_{\text{trend}} < 0.001$; total milk, 5–7 servings/week versus <4/month, HR = 0.39, 95% CI: 0.22–0.68, $P_{\text{trend}} = 0.01$; skim/low fat milk, 5–7 servings/week versus <4/month, HR = 0.39, 95% CI: 0.22–0.69, $P_{\text{trend}} = 0.01$). There was a non-significant inverse association for endometrioid EOC for the highest category of total milk or skim/low fat milk intake (>1 serving/day); however, this was based on a small number of cases (7 and 6 cases, respectively). In contrast, there was no association between lactose or milk intake in adulthood and risk of serous/poorly differentiated EOC.

To test whether the consumption of dairy nutrients or milk during an earlier life period was related to the later risk of EOC, we evaluated the reported intake during high school and observed a significant trend of decreasing risk with increasing intake of dairy fat ($P_{\text{trend}} =$

0.04) although the individual quintile estimates were not statistically significant (Table 4). There was no association between intake of lactose, dairy calcium or any type of milk intake during high school and EOC risk. We also evaluated the cumulative average intake in quartiles due to small numbers of dairy nutrients and milk during premenopausal or postmenopausal time periods in relation to risk of premenopausal disease (for premenopausal diet) and/or postmenopausal disease. These analyses highlighted a significant inverse association for high intake of skim/low fat milk after menopause and risk of postmenopausal EOC (5 servings/week skim/low fat milk versus <4/month, HR = 0.76, 95% CI: 0.59–0.97, $P_{\text{trend}} = 0.02$) (Online resource Table S1). We also observed an inverse association between premenopausal skim/low fat milk intake and risk of EOC overall (Q4 versus Q1, HR = 0.76, 95% CI: 0.59 – 1.00, $P_{\text{trend}} = 0.04$). We observed no association between premenopausal dairy nutrient or milk consumption in relation to risk of premenopausal or postmenopausal EOC although due to the small number of cases these analyses were exploratory.

We carried out a latency analysis to evaluate the risk of EOC in relation to the simple updated dietary intake that occurred at various time periods (from 0–4 years to 12–16 years) prior to diagnosis. We observed significant inverse associations with EOC risk for high intakes of lactose and milk (total milk or skim/low fat) that occurred 8–12 years before diagnosis (lactose, Q5 versus Q1, HR = 0.73, 95% CI: 0.55–0.97, $P_{\text{trend}} = 0.03$; total milk, >1 serving/day versus <4/month, HR = 0.70, 95% CI: 0.52–0.95, $P_{\text{trend}} = 0.04$; skim/low fat milk, >1 serving/day versus <4/month, HR = 0.71, 95% CI: 0.53–0.95, $P_{\text{trend}} = 0.03$) (Table 5). For dietary intake that occurred 4–8 years prior to diagnosis, we observed a similar but non-significant inverse association with EOC risk with increased consumption of lactose and milk.

Based on previous suggestions that increased consumption of lactose may be associated with poorer survival, we used Cox proportional hazards competing risks analysis to estimate the risk associations for dairy nutrient (lactose, dairy calcium, dairy fat) or milk (total milk and skim/low fat milk) intake with rapidly fatal versus less aggressive EOC; rapidly fatal cases were those who died ≤3 years from their date of diagnosis while less aggressive cases died >3 years post-diagnosis or were still alive. We observed no statistically significant differences in the risk associations between the rapidly fatal and the less aggressive cases (data not shown).

Conclusions

In the current study we evaluated the association of dairy nutrients (lactose, dairy calcium, dairy fat) and milk intake in relation to risk of EOC overall and for serous and endometrioid invasive EOC. This analysis updates a previous report in the NHS and adds data from the NHSII. To our knowledge this was the first study to assess dairy nutrient and milk consumption during specified life periods (high school, premenopause/postmenopause) as well as considering the latency between the reported diet in relation to the risk of EOC. We did not observe positive associations between lactose or milk intake and risk of EOC overall, but we observed an inverse association with risk of endometrioid tumors.

It has been hypothesized that lactose (and its metabolite galactose) may increase ovarian cancer risk through its toxic effects on the ovarian germ cells, leading to subsequent gonadotropin stimulation of the ovaries [31]. In the current study there was no association between the cumulative average intake of lactose with risk of EOC overall (including borderline and invasive tumors). We replicated our previous findings from the earlier report (evaluation of the cumulative average lactose intake from 1980–1990 with follow-up through 1996 in the NHS) of increased risk for serous/poorly differentiated EOC with high lactose intake (data not shown) [7]. Similar methods were used in both studies (including the evaluation of the cumulative updated diet). The difference in results between the current and previous report is likely due to the longer period of follow-up (28 years of follow-up versus 16 years in the previous report) and the corresponding increase in sample size (e.g., 403 serous/poorly differentiated tumors were evaluated versus 174 in the previous report) including the addition of participants from the NHSII in the current report. Based on this larger sample size, the currently observed association provides our best estimate of the relationship between lactose intake and ovarian cancer risk. Other previous prospective studies have found no association [32,33] or a positive association [5,34,35] between lactose intake and EOC risk. The pooled analysis of 12 cohort studies (including the NHS) reported a 19% increased risk for invasive EOC with a higher intake of lactose (> 30 g/day versus <10) [5].

In analyses of the cumulative average intake of dairy calcium and dairy fat, we observed no significant association with risk of EOC. Few cohort studies have evaluated calcium intake in relation to EOC risk and results have been heterogeneous; consistent with the current study, the pooled analysis of cohort studies (including the NHS) reported no association with calcium intake [5], while other studies reported a significant inverse association [32] or a non-significant elevation in risk [34] for EOC with high calcium intake. In one other prospective study that evaluated dairy fat intake, an increased risk for invasive EOC was observed [33]. Current data suggest no association or a very modest association with dairy calcium or dairy fat.

There also was no significant association between the cumulative average intake of milk (skim/low fat milk, whole milk or total milk [skim plus whole]) and EOC risk. Milk intake has been examined in several previous cohort studies with heterogeneous results. Consistent with our findings, the Netherlands Cohort Study [33] and the pooled analysis of 12 cohort studies [5] observed no association with intake of any type of milk, while other studies reported a non-significant increased risk of EOC with high consumption of skim milk [34] or total milk (invasive tumors only) [35]. It is important to note that the other prospective analyses have used a single dietary assessment often occurring at the study baseline; hence the time period of dairy nutrient/milk intake differs from the cumulative average intake that was evaluated in the current study.

Interestingly the association of dairy nutrients and milk intake in relation to risk of EOC differed across histologic subtypes. Specifically, there was no association with risk of serous tumors while there was an inverse association with risk of endometrioid tumors with a high intake of lactose or total milk; the latter observation is based on a small number ($n=101$) of endometrioid invasive EOCs thus further confirmation of these associations is needed by

pooling data from multiple studies. Our finding of no association between lactose intake and serous invasive EOC contrasts with results from the Swedish Mammography Cohort, in which a stronger increased risk for serous invasive EOC with high lactose intake was observed as compared with non-serous epithelial tumors [35]. The pooled analysis did not observe any difference in the associations with dairy nutrients (including lactose) and milk intake when comparing serous, endometrioid and mucinous invasive EOCs [5].

To our knowledge this is the first report of a decreased risk for endometrioid EOC with a high intake of lactose or milk. Although the pooling project did not observe an inverse association with risk of endometrioid tumors [5], the inclusion of the NHSII cohort in our study may have led to a higher proportion of endometrioid tumors in younger women compared to previous studies. Interestingly, in an analyses of dairy foods and nutrient intake in relation to risk of laparoscopically-confirmed endometriosis, which may be a precursor lesion for endometrioid EOC [36–39], in the NHSII, an increased intake of dairy foods was associated with a decreased risk of endometriosis [40]. Two previous case-control studies evaluated the association between dairy food/milk intake and laparoscopically-confirmed endometriosis: a population-based study observed a non-significant inverse association between total dairy food intake and endometriosis [41], while no association with total milk intake was noted in another study that used hospital-based controls [42]. A mechanism that may link high dairy food intake with reduced risk of endometriosis, and also possibly reduced risk for endometrioid EOC, is the decrease in oxidative and inflammatory stress associated with a high dairy intake. In support of this mechanism, a study in mice showed that a high milk diet reduced reactive oxygen species production in adipose tissues [43]. However, it remains to be determined how a diet high in dairy intake may influence the hormonal and inflammatory milieu of the endometrium and peritoneum. Another possible mechanism is that milk contains relatively high levels of progesterone, although it has been noted that steroid hormones obtained from food are thought to be minor when compared to a person's endogenous production [44]. An inverse association between higher levels of progesterone and endometriosis/endometrioid EOC is biologically plausible because progestins are commonly used in the treatment of endometriosis to inhibit the growth and activity of endometriotic implants [45]. Additional studies are needed to confirm whether a high intake of lactose or milk decreases risk for endometrioid EOC and to investigate the biologic mechanisms that may explain this association.

We also evaluated dairy nutrient and milk intake during specific periods of life in relation to risk of EOC overall. We observed that consumption of milk or most dairy nutrients during high school was not related to the later risk of EOC. When considering intake of lactose, dairy calcium, dairy fat or milk during premenopause or postmenopause, we observed that a high intake of skim/low fat milk during postmenopause was inversely associated with risk of postmenopausal EOC; however, analyses of premenopausal and postmenopausal disease limit the number of cases hence these findings require confirmation in additional studies.

We carried out latency analyses to evaluate whether the consumption of lactose, dairy calcium, dairy fat and milk at specific time periods (from 0 to 16 years preceding diagnosis) was related to the risk of EOC overall. These analyses highlight significant inverse associations with high consumption of lactose or milk (total milk or skim/low fat) that

occurred 8–12 years before the diagnosis of disease while there was no association with recent intake. These findings require confirmation in additional studies before drawing any firm conclusions.

A previous study suggested that increased consumption of lactose may be associated with poorer survival [46]. We did not observe an association with rapidly fatal disease, but observed a suggestive inverse association between intake of lactose and risk for less aggressive disease; the latter observation may be due to the higher proportion of endometrioid tumors in the less aggressive case subgroup.

This study has advantages and disadvantages that should be considered when interpreting these findings. Since dietary intakes and other exposure information were collected prospectively, this minimizes the likelihood of differential misclassification with respect to ovarian cancer diagnosis. Although non-differential misclassification of exposure may result from self-reported dietary data, subjects were asked to report dietary intakes for the previous year, which can measure relatively long-term diet while minimizing the effects of short-term variation in diet. We have obtained repeated measurements of diet over time, hence this allowed the assessment of the cumulative average diet, which reduces the influence of within-subject variation. Misclassification of the ovarian cancer diagnosis is unlikely because participants report cancer incidence with a high degree of accuracy and other sources (e.g., National Death Index, SEER cancer registry) were used to confirm the diagnosis. The medical record review of all cases by a gynecologic pathologist further minimizes any potential inaccuracies in classifying cases according to the tumor histologic subtype or behavior. These cohorts do not represent a random sample of U.S. women and therefore the dietary and other lifestyle characteristics may not reflect those in the general population. However, the associations identified should be generalizable because the biologic effects of dietary variables should be the same as those in the general population. In this study, we considered milk intake in relation to its fat content (skim/low fat milk and whole milk); however, since very few participants reported consuming whole milk in adulthood, analyses of whole milk intake were limited by the small sample size. Since the dairy nutrients (lactose, dairy calcium and dairy fat) are highly correlated, it is difficult to evaluate their independent associations with EOC risk. However, we focused *a priori* on lactose due to the hypothesized toxic effects of unmetabolized galactose on the ovaries. We cannot, however, exclude the possibility that components of dairy foods other than lactose, dairy calcium or dairy fat may explain the observed associations with ovarian cancer risk.

In summary, we observed no association between the cumulative average intake of lactose in adulthood and EOC risk overall. In analyses comparing the different histologic subtypes of invasive EOC, there was an inverse association with a high intake of lactose and risk of endometrioid EOC while there was no association with serous EOC risk. We observed that lactose or milk intake assessed at specific time periods throughout life (e.g., postmenopause or 8–12 years before diagnosis) may be inversely associated with risk of EOC; however these analyses require confirmation in additional studies. We did not observe an association between most dairy nutrients or milk intake during high school and later risk of EOC. These results do not support the hypothesis that a high lactose intake increases risk for EOC, and highlights a possible inverse association for endometrioid EOC. The potential inverse

association between lactose intake and risk of endometrioid EOC and similar observations in a recent study of endometriosis provides an interesting biological hypothesis to test in further studies; these findings require confirmation in additional studies to determine if they could be useful for the prevention of endometrioid EOC.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Age-standardized characteristics of participants in the Nurses' Health Study (NHS) in 1994 and the NHSII in 2001, the midpoint of each follow-up period (1980–2008 for the NHS and 1991–2009 for the NHSII)

	NHS					NHSII				
	Quintiles of lactose intake					Quintiles of lactose intake				
	Q1	Q2	Q3	Q4	Q5	Q1	Q2	Q3	Q4	Q5
Sample size	10328	12789	12954	12807	11795	15193	16013	16191	16339	15555
Means										
Age (y)	59.3(6.9)	59.2(7.1)	59.5(7.2)	59.6(7.2)	60.2(7.3)	46.6(4.6)	46.2(4.6)	45.9(4.6)	45.6(4.7)	45.6(4.7)
Duration OC use (y)	2.2(3.5)	2.1(3.5)	2.1(3.4)	2.0(3.4)	2.0(3.4)	4.8(5.0)	4.8(5.0)	4.9(5.0)	4.7(4.9)	4.6(4.9)
BMI (kg/m ²)	26.1(5.3)	26.3(5.2)	26.5(5.2)	26.5(5.1)	26.4(5.2)	26.7(6.5)	27.0(6.6)	26.8(6.2)	26.7(6.1)	26.5(6.1)
Percentages										
Parous	95	95	95	95	95	80	81	81	82	83
Postmenopausal	79	79	79	79	78	15	15	14	15	14
Tubal ligation	22	21	21	21	20	28	27	26	25	24
Family history ovarian cancer	2	2	2	3	2	2	2	2	2	2
Mean daily intake										
Dairy calcium (mg)	204.6(85.5)	298.9(66.8)	395.4(66.2)	511.6(72.1)	753.8(170.5)	256.5(93.3)	381.2(75.6)	497.2(74.8)	646.0(83.2)	947.8(196.9)
Dairy fat (g)	10.3(5.3)	11.2(4.4)	11.9(4.3)	12.7(4.3)	14.4(5.1)	11.0(5.3)	12.0(4.6)	12.2(4.5)	12.9(4.6)	14.2(5.1)
Total calories (kcal)	1659(459)	1742(437)	1743(422)	1718(421)	1639(391)	1794(518)	1849(495)	1826(473)	1836(504)	1741(426)

Note: Values are means (SD) or percentages and are standardized to the age distribution of the study population. All factors except age were age standardized in 5-year intervals for each cohort.

Table 2

Adjusted Hazard Ratios (HRs) for EOC associated with the cumulative average intake of dairy nutrients and foods in adulthood (2–6 years between exposure and outcome) in the NHS/NHSII

Dairy nutrients	Category of intake ^d					<i>P</i> _{trend} ^b
	Q1	Q2	Q3	Q4	Q5	
Lactose (g/d)						
Range	(0 – 6.3)	(6.3 – 10.8)	(10.8 – 15.6)	(15.6 – 22.9)	(22.9 – 216.4)	
Cases/Person-years, n	176/518334	165/517580	156/517314	145/517224	122/517686	
Model 1 ^c	1.00 (Ref)	0.97 (0.78–1.20)	0.93 (0.75–1.16)	0.91 (0.73–1.14)	0.88 (0.69–1.11)	0.23
Model 2 ^{c,d}	1.00 (Ref)	0.97 (0.78–1.20)	0.92 (0.74–1.15)	0.91 (0.72–1.13)	0.87 (0.69–1.11)	0.22
Dairy calcium (mg/d)						
Range	(0 – 277.7)	(277.7 – 387.8)	(387.8 – 504.4)	(504.4 – 675.4)	(675.4 – 4557.0)	
Cases/Person-years, n	171/517942	172/517579	164/517227	148/517331	109/518060	
Model 1 ^c	1.00 (Ref)	1.05 (0.85–1.30)	1.04 (0.84–1.30)	0.99 (0.79–1.23)	0.86 (0.68–1.10)	0.18
Model 2 ^{c,d}	1.00 (Ref)	1.05 (0.85–1.30)	1.04 (0.84–1.29)	0.98 (0.79–1.23)	0.86 (0.68–1.10)	0.18
Dairy fat (g/d)						
Range	(0 – 8.4)	(8.4 – 10.7)	(10.7 – 13.0)	(13.0 – 16.3)	(16.3 – 118.2)	
Cases/Person-years, n	157/517719	151/517477	172/517448	146/517628	138/517866	
Model 1 ^c	1.00 (Ref)	0.98 (0.78–1.23)	1.15 (0.92–1.43)	1.01 (0.81–1.27)	1.00 (0.79–1.26)	0.99
Model 2 ^{c,d}	1.00 (Ref)	0.98 (0.79–1.23)	1.16 (0.93–1.44)	1.03 (0.82–1.29)	1.01 (0.80–1.27)	0.91
Dairy foods						
	<4/month	1/wk	2–4/wk	5–7/wk	>1/day	
Total milk^e (8 oz glass)						
Cases/Person-years, n	116/381357	132 382290	169/536548	289/979667	52/270935	
Model 1 ^c	1.00 (Ref)	1.08 (0.84–1.39)	1.05 (0.82–1.33)	0.96 (0.77–1.20)	0.80 (0.57–1.13)	0.09
Model 2 ^{c,d}	1.00 (Ref)	1.07 (0.83–1.38)	1.04 (0.82–1.33)	0.95 (0.76–1.19)	0.80 (0.57–1.13)	0.09
Skim/low fat milk (8 oz glass)						
Cases/Person-years, n	198/577092	129/389913	154/506986	234/843183	43/233622	
Model 1 ^c	1.00 (Ref)	0.90 (0.72–1.13)	0.91 (0.73–1.13)	0.83 (0.69–1.02)	0.75 (0.53–1.05)	0.05
Model 2 ^{c,d}	1.00 (Ref)	0.90 (0.72–1.13)	0.91 (0.73–1.13)	0.83 (0.68–1.01)	0.76 (0.54–1.06)	0.05

Dairy nutrients	Category of intake ^a					<i>P</i> _{trend} ^b
	Q1	Q2	Q3	Q4	Q5	
Whole milk (8 oz glass)						
Cases/Person-years, <i>n</i>	567/2038760	99/245506	44/134281	41/112858	7/19392	
Model 1 ^c	1.00 (Ref)	1.13 (0.91–1.40)	0.97 (0.71–1.32)	1.14 (0.83–1.58)	1.29 (0.60–2.75)	0.33
Model 2 ^{c,d}	1.00 (Ref)	1.12 (0.90–1.40)	0.97 (0.71–1.33)	1.15 (0.83–1.59)	1.29 (0.60–2.76)	0.33

^aData are Hazard Ratios (95% CI) unless indicated otherwise.

^b*P*-value test for trend using a trend variable based on the median of each category of intake.

^cModel 1 was adjusted for total caloric intake (continuous). Model 2 was adjusted for total caloric intake (continuous), number of pregnancies (continuous) and parity (ever/never), oral contraceptive pill use (0, <1 yr (ref), 1 – <5 yrs, 5 yrs), menopausal status (post vs pre/perimenopausal), tubal ligation and family history of ovarian cancer (yes vs no). All models were stratified by age in months, cohort, and time period.

^d*P*-values for heterogeneity (*P*_{het}) between studies were 0.17.

^eTotal milk intake is the sum of skim/low fat and whole milk intakes.

Table 3

Associations between the cumulative average intake of lactose and milk (2–6 years between exposure and outcome) in adulthood and risk of invasive EOC by tumor histology in the NHS/NHSII

Serous/poorly differentiated (n = 403 ^a)		Endometrioid (n =101)		
Cases/Person-years	Adjusted HR ^b (95% CI)	Cases/Person-years	Adjusted HR ^b (95% CI)	P ^{het c}
Dairy nutrients				
Lactose (g/d) ^d				
Q1	80/518421	1.00 (Ref)	36/518456	1.00 (Ref)
Q2	87/517644	1.11 (0.82–1.50)	25/517695	0.70 (0.42 – 1.18)
Q3	85/517380	1.11 (0.81 –1.51)	17/517444	0.48 (0.27 – 0.87)
Q4	83/517278	1.16 (0.85 –1.58)	13/517335	0.38 (0.20 – 0.72)
Q5	68/517729	1.12 (0.81–1.55)	10/517772	0.32 (0.16 – 0.65)
P _{trend} ^e		0.50		< 0.001
Dairy foods				
Total milk ^{d,f} (8 oz glass)				
<4/month	50/381412	1.00 (Ref)	25/381435	1.00 (Ref)
1/wk	65/382356	1.20 (0.83 – 1.74)	16/382394	0.62 (0.33 – 1.16)
2–4/wk	89/536612	1.25 (0.88 – 1.77)	28/536669	0.81 (0.47 – 1.39)
5–7/wk	164/979778	1.20 (0.86 – 1.65)	25/979885	0.39 (0.22 – 0.68)
>1/day	31/270952	1.12 (0.71 – 1.78)	7/270973	0.47 (0.20 – 1.10)
P _{trend} ^e		0.82		0.01
Skim/low fat milk ^d (8 oz glass)				
<4/month	93/579059	1.00 (Ref)	34/579112	1.00 (Ref)
1/wk	65/391569	0.96 (0.70 – 1.33)	17/391603	0.72 (0.40 – 1.29)
2–4/wk	86/511130	1.09 (0.81 – 1.47)	25/511184	0.86 (0.51 – 1.45)
5–7/wk	132/853073	0.98 (0.75 – 1.29)	19/855160	0.39 (0.22 – 0.69)
>1/day	26/238742	1.01 (0.65 – 1.57)	6/238762	0.55 (0.23 – 1.31)
P _{trend} ^e		0.97		0.01

^aNumbers may not add up to total in analyses of milk intake due to missing data.

^bData are Hazard Ratios (95% CI) unless indicated otherwise.

^cThe P -value for heterogeneity (P_{het}) is from the likelihood-ratio test that compares a model with the same estimate for the association with the exposure of interest (e.g., quintiles of lactose intake) across histologic subtypes to a model which allows the association with the exposure of interest to vary across histologic subtypes.

^dModels were adjusted for total caloric intake (continuous), number of pregnancies (continuous) and parity (ever/never), oral contraceptive pill use (0, <1 yr (ref), 1 – <5 yrs, 5 yrs), menopausal status (post vs pre/perimenopausal) and tubal ligation (yes vs no). All models were stratified by age in months, cohort and time period. Models were not adjusted for family history of ovarian cancer due to small numbers in the endometrioid category. The associations with age and parity were allowed to vary by histologic subtype in the models.

^e P -value test for trend using a trend variable based on the median value for each category of intake.

^fTotal milk is the sum of whole milk and skim/low fat milk intake.

Table 4

Adjusted Hazard Ratios (HRs) for EOC associated with intake of dairy foods and nutrients during high school in the NHS/NHSII

Dairy nutrients	Category of intake ^a					<i>P</i> _{trend} ^b
	Q1	Q2	Q3	Q4	Q5	
Lactose (g/d)						
Range ^c	(0 – 14.3)	(14.3 – 22.1)	(22.1–29.9)	(29.9–39.0)	(39.0–171.0)	
Cases/Person-years, <i>n</i> ^c	103/257587	110/257212	117/257579	89/257312	76/257586	
NHS ^d	1.00 (Ref)	1.17 (0.88–1.56)	1.16 (0.88–1.54)	0.96 (0.71–1.29)	0.81 (0.59–1.11)	0.09
NHSII ^d	1.00 (Ref)	1.24 (0.50–3.07)	1.36 (0.53–3.48)	0.54 (0.16–1.81)	0.96 (0.38–2.43)	0.54
Combined ^{d,e}	1.00 (Ref)	1.18 (0.89–1.54)	1.17 (0.89–1.53)	0.92 (0.69–1.23)	0.82 (0.61–1.11)	0.06
Dairy calcium (mg/d)						
Range ^c	(0 – 433)	(434 – 618)	(619–803)	(804–1017)	(1018–3759)	
Cases/Person-years, <i>n</i> ^c	100/256985	114/257592	111/258273	99/256671	71/257754	
NHS ^d	1.00 (Ref)	1.23 (0.92–1.63)	1.13 (0.85–1.51)	1.06 (0.79–1.43)	0.79 (0.57–1.10)	0.11
NHSII ^d	1.00 (Ref)	1.04 (0.43–2.55)	1.03 (0.40–2.70)	0.77 (0.27–2.21)	0.82 (0.34–2.00)	0.52
Combined ^{d,e}	1.00 (Ref)	1.21 (0.92–1.59)	1.12 (0.85–1.47)	1.04 (0.78–1.37)	0.80 (0.59–1.09)	0.08
Dairy fat (g/d)						
Range ^c	(0 – 16.9)	(16.9 – 24.1)	(24.1 – 30.6)	(30.6 – 38.4)	(38.4 – 150.9)	
Cases/Person-years, <i>n</i> ^c	110/257440	115/257613	88/257504	90/257547	92/257171	
NHS ^d	1.00 (Ref)	1.16 (0.88–1.52)	0.79 (0.58–1.06)	0.80 (0.59–1.07)	0.82 (0.61–1.10)	0.03
NHSII ^d	1.00 (Ref)	0.57 (0.18–1.79)	0.99 (0.35–2.77)	1.08 (0.39–3.00)	0.84 (0.30–2.31)	0.85
Combined ^{d,e}	1.00 (Ref)	1.10 (0.85–1.44)	0.80 (0.60–1.07)	0.82 (0.62–1.09)	0.82 (0.62–1.09)	0.04
Dairy foods	<4/month	1/wk	2–4/wk	5–7/wk	>1/day	<i>P</i> _{trend} ^b
Total milk ^f (8 oz glass)						
Cases/Person-years, <i>n</i> ^c	59/146293	28/56874	62/128400	135/357114	194/558465	
NHS ^d	1.00 (Ref)	1.41 (0.87–2.27)	1.26 (0.86–1.85)	1.03 (0.74–1.42)	0.97 (0.69–1.37)	0.29
Combined ^{d,e}	1.00 (Ref)	1.37 (0.87–2.16)	1.29 (0.90–1.85)	1.02 (0.75–1.40)	0.97 (0.70–1.34)	0.24

Dairy nutrients	Category of intake ^a					<i>P</i> _{trend} ^b
	Q1	Q2	Q3	Q4	Q5	
Skim/low fat milk (8 oz glass)						
Cases/Person-years, <i>n</i> ^c	402/890281	6/13958	7/26292	18/59019	18/74385	
NHS ^d	1.00 (Ref)	0.90 (0.33–2.45)	0.87 (0.39–1.96)	0.96 (0.55–1.67)	0.97 (0.55–1.69)	0.85
Combined ^{d,e}	1.00 (Ref)	1.15 (0.50–2.62)	0.85 (0.40–1.82)	1.01 (0.62–1.66)	0.93 (0.56–1.54)	0.78
Whole milk (8 oz glass)						
Cases/Person-years, <i>n</i> ^c	82/199151	23/50298	62/117761	130/313893	180/497244	
NHS ^d	1.00 (Ref)	1.19 (0.74–1.92)	1.22 (0.86–1.73)	1.03 (0.77–1.37)	0.92 (0.68–1.24)	0.24
Combined ^{d,e}	1.00 (Ref)	1.17 (0.74–1.87)	1.30 (0.93–1.82)	1.05 (0.79–1.39)	0.94 (0.70–1.26)	0.25

^aData are Hazard Ratios (95% CI) associated with quintiles of intake (Q1–Q5) or categories of intake unless indicated otherwise.

^b*P*-value test for trend using a trend variable based on the median value from each category of intake.

^cNumbers refer to the combined NHS/NHSII analysis.

^dMultivariate models were adjusted for total caloric intake (continuous), number of pregnancies (continuous) and parity (ever/never), oral contraceptive use (0, <1 yr (ref), 1 – <5 yrs, 5 yrs), menopausal status (post vs pre/perimenopausal), tubal ligation and family history of ovarian cancer (yes vs no). All models were stratified by age in months, cohort (in the combined analyses) and time period. Due to small numbers, the risk estimates are not shown for milk intake in the NHSII, and the multivariate models for the NHS and NHSII when analyzed separately were adjusted for all of the factors mentioned in ^d except for family history of ovarian cancer.

^e*P*-values for heterogeneity between studies were 0.41.

^fTotal milk intake is the sum of skim/low fat and whole milk intake.

Table 5

Adjusted Hazard Ratios (HRs) for EOC according to intake of lactose and milk using varying lag times^a between the dietary intake and follow-up in the NHS/NHSII.

	Baseline		Simple update							
	Cases, <i>n</i>		Cases, <i>n</i>	12–16 yr lag	Cases, <i>n</i>	8–12 yr lag	Cases, <i>n</i>	4–8 yr lag	Cases, <i>n</i>	0–4 yr lag
Lactose <i>b</i> (g/d)										
Q1	209	1.00 (Ref)	86	1.00 (Ref)	129	1.00 (Ref)	155	1.00 (Ref)	165	1.00 (Ref)
Q2	165	0.96 (0.78–1.19)	103	1.23 (0.92–1.65)	128	1.03 (0.81–1.32)	136	0.88 (0.70–1.11)	159	0.97 (0.78–1.21)
Q3	166	1.02 (0.83–1.26)	85	1.04 (0.77–1.41)	114	0.94 (0.73–1.21)	144	0.93 (0.74–1.17)	147	0.91 (0.73–1.14)
Q4	185	1.16 (0.95–1.42)	89	1.14 (0.84–1.54)	116	1.00 (0.77–1.28)	109	0.74 (0.58–0.95)	149	0.94 (0.75–1.17)
Q5	143	0.97 (0.79–1.21)	74	1.10 (0.80–1.51)	78	0.73 (0.55–0.97)	116	0.85 (0.66–1.08)	134	0.90 (0.71–1.13)
P _{trend} ^c		0.74		0.83		0.03		0.13		0.38
Dairy foods										
Total milk <i>b_{i,d}</i> (8 oz glass)										
<4/month	202	1.00 (Ref)	76	1.00 (Ref)	125	1.00 (Ref)	119	1.00 (Ref)	148	1.00 (Ref)
1/wk	65	0.82 (0.62–1.09)	40	1.28 (0.86–1.89)	45	0.88 (0.62–1.24)	59	1.23 (0.90–1.69)	58	0.99 (0.73–1.35)
2–4/wk	141	1.02 (0.82–1.27)	94	1.51 (1.11–2.06)	90	0.83 (0.63–1.09)	119	1.18 (0.91–1.54)	130	1.03 (0.81–1.31)
5–7/wk	264	0.96 (0.80–1.16)	134	1.07 (0.80–1.43)	176	0.85 (0.67–1.07)	197	1.00 (0.79–1.27)	216	0.90 (0.73–1.12)
>1/day	127	0.96 (0.76–1.22)	72	1.13 (0.81–1.59)	74	0.70 (0.52–0.95)	85	0.88 (0.66–1.18)	102	0.84 (0.65–1.10)
P _{trend} ^c		0.90		0.72		0.04		0.10		0.13
Skim/low fat milk <i>b_i</i> (8 oz glass)										
<4/month	343	1.00 (Ref)	130	1.00 (Ref)	175	1.00 (Ref)	181	1.00 (Ref)	202	1.00 (Ref)
1/wk	42	0.76 (0.55–1.06)	27	1.01 (0.66–1.55)	38	0.97 (0.68–1.39)	47	1.16 (0.84–1.60)	49	1.06 (0.77–1.45)
2–4/wk	107	0.96 (0.77–1.19)	74	1.21 (0.91–1.62)	74	0.77 (0.59–1.02)	101	1.00 (0.78–1.29)	109	0.94 (0.74–1.20)
5–7/wk	197	0.91 (0.76–1.09)	117	0.96 (0.74–1.24)	155	0.86 (0.69–1.08)	170	0.89 (0.72–1.10)	198	0.90 (0.74–1.11)
>1/day	110	0.97 (0.77–1.21)	68	1.04 (0.76–1.41)	68	0.71 (0.53–0.95)	80	0.80 (0.61–1.05)	96	0.83 (0.65–1.08)
P _{trend} ^c		0.49		0.92		0.03		0.05		0.12

^aValues shown are multivariate Hazard Ratios (95% CI) in the combined NHS/NHSII. Follow-up years were 1980–2008 in the NHS and 1991–2009 in the NHSII for the 0–4 year lag, 1984–2008 in the NHS and 1995–2009 in the NHSII for the 4–8 year lag, 1988–2008 in the NHS and 1999–2009 in the NHSII for the 8–12 year lag, and 1992–2008 in the NHS and 2003–2009 in the NHSII for the 12–16 year lag.

^b Multivariate models were adjusted for total caloric intake at the relevant time period (continuous), number of pregnancies (continuous) and parity (ever/never), oral contraceptive pill use (0, <1 yr (ref), 1 – <5 yrs, ≥ 5 yrs), menopausal status (post vs pre/perimenopausal), tubal ligation and family history of ovarian cancer (yes vs no). All models were stratified by age in months, cohort and time period.

^c *P*-value test for trend using a trend variable based on the median value for each category of intake.

^d Total milk is the sum of whole milk and skim/low fat milk intake.