Published in final edited form as:
Int J Cancer. 2012 June 1; 130(11): 2664–2671. doi:10.1002/ijc.26265.

Milk, dairy intake and risk of endometrial cancer: a twenty six-year follow-up

Davaasambuu Ganmaa, **Xiaohui Cui**, **Diane Feskanich**, **Susan E. Hankinson**, and **Walter C. Willett**

Abstract

Background—Estrogens have a central role in the etiology of endometrial cancer. Milk and dairy products are a source of steroid hormones and growth factors that might have physiological effects in humans. We hypothesized that high intakes of milk and dairy products are associated with an increased risk of endometrial cancer, particularly among postmenopausal women not using hormone therapy.

Methods—This was a prospective cohort study with 68,019 female participants in the Nurses' Health Study aged 34–59 in 1980. Milk and dairy consumption were assessed in 1980, 1984, 1986, 1990, 1994, 1998, and 2002 as servings per day and the follow-up continued through 2006.

Results—The multivariate relative risks of adenocarcinoma of the endometrium across categories of cumulatively averaged total dairy consumption compared with < 1 svg/d were: 0.94 (95% CI 0.71–1.25) for 1–1.4 svg/day, 1.14 (0.87–1.49) for 1.5–1.9 svg/day, 1.10 (0.84–1.44) for 2–2.9 svg/day, 1.26 (0.94–1.70) for ≥3 svg/day) (p for trend= 0.06). The association between total dairy intake and endometrial cancer was significant only among the post-menopausal women (for ≥3 svg/day RR = 1.41, 95% CI 1.01 – 1.98, p for trend=0.02) and was evident only among those who were not currently using hormone therapy (RR = 1.58, 95% CI 1.05–2.36, p for trend=0.003). Total dairy intake was not significantly associated with risk of pre-invasive endometrial cancer.

Conclusion—We observed a marginally significant overall association between dairy intake and endometrial cancer and a stronger association among postmenopausal women who were not using estrogen-containing hormones.

Keywords

milk; dairy products; endometrial cancer; estrogen and progesterone

INTRODUCTION

Estrogens mediate cellular growth and differentiation in both endometrial tissue and mammary glands, and exposure to estrogens increase risks of breast and endometrial cancers (1). Endometrial cancer is particularly sensitive and thus it can serve as a useful indicator of estrogenic stimulation by diet or drugs (2). Milk contains measurable amounts of steroid hormones, including estrogens (3), and thus milk consumption at critical points in life could affect the risk of endometrial cancer. The seven-day feeding of ovariectomized adult and sexually immature rats with commercially available low-fat milk (less than 1% fat content) increased the weight of uteri almost as much as a 0.1-ug/ml estrone sulfate solution (3). However, plasma estrogen levels in prepubertal girls remained similar before and after one week and one month of milk feeding in our pilot studies (4).

To address the hypothesis that long term dairy consumption might increase the risk of estrogen-sensitive cancers, we examined the relation of milk and dairy food consumption to risk of endometrial cancer prospectively in a large population of women with long follow-up

and repeated measures of diet. We specifically examined postmenopausal women not using hormone therapy because an effect of diet would most likely be seen among those without other major sources of sex hormones.

METHODS

Study Population

The Nurses' Health Study cohort was established in 1976 when 121 700 female registered nurses from 11 states in the USA between ages 30 and 55 answered a mailed questionnaire on lifestyles and potential risk factors for cancer and other diseases. Follow-up questionnaires have been mailed every two years to update the information on risk factors and major medical events. The follow-up rate through 2006, as a percent of total possible person-years, was 95%. Deaths in the cohort are identified by reports from family members and the US Postal Service, and a search of the National Death Index; at least 98% of deaths are ascertained (5).

The current study was approved by the Institutional Review Board at the Brigham and Women's Hospital. At 1980 baseline, we excluded women who had hysterectomy (n=20,612), did not respond to 1980 food frequency questionnaire (FFQ) or had more than 10 missing items or a total energy intake <500 or >3500 kcal/day (n=28,487), had died before 1980 (n=747), or had reported any type of cancer before 1980 (excluding nomelanoma skin cancer, n=3,660). Since obesity is an important risk factor for endometrial cancer, we also excluded women with missing body mass index (BMI) at baseline (n=166, these women could reenter the analysis in subsequent cycles once information on BMI was available). A total of 68,019 women remained for analysis.

Exposure Assessment—Diet was assessed by a semi-quantitative food frequency questionnaire (FFQ) first administered in 1980. For each food item, the questionnaire specified a common serving size. In 1980, dairy foods on the FFQ included low fat or skim milk (8 oz glass, 240mL), whole milk (8 oz glass, 240mL), hard cheeses (slice or 1oz serving, 28 g), cottage cheese (1/2 cup, 120mL), ice cream (1/2 cup, 120mL), yogurt (1 cup) and butter (number of pats). An expanded food-frequency questionnaire (approximately 130 foods) was used in 1984 (6) and later years with additional questions assessing the intake of sour cream (1 tablespoon, 15ml), cream (tablespoon, 15 ml), sherbet (1/2 cup, 120mL), cream cheese (1 oz, 28g), and other cheese (1 oz, 28g). Dietary assessments were repeated in 1984, 1986, 1990, 1994, 1998 and 2002. For each item, participants were asked how often, on average, they had consumed the specified amount of each beverage or food over the past year. The participants could choose from nine pre-specified frequency categories (never, 1 to 3 per month, 1 per week, 2 to 4 per week, 5 to 6 per week, 1 per day, 2 to 3 per day, 4 to 5 per day, and 6 or more per day). For each food on the 1980 FFQ, participants were asked if their use had greatly increased or decreased over the past 10 years. Details of the semiquantitative FFQ and documentation of its reproducibility and validity have been published elsewhere (6,7). Nutrient intakes (i.e. calcium, vitamin D, protein, alcohol) were calculated based on the nutrient content of foods derived primarily from the US Department of Agriculture sources and supplemented with data from food manufacturers and published research. In a validation study among a subsample of our cohort, we found high correlations between intakes assessed by FFQ and by diet records: 0.81 for skim or low-fat milk, 0.62 for whole milk, 0.85 for butter, 0.73 for ice cream, 0.80 for cottage cheese, 0.57 for hard cheese, 0.85 for butter, and 0.94 for yogurt (6, 8).

Identification of endometrial cancer cases—On all biennial questionnaires, participants were asked to report any new diagnosis of endometrial cancer. From June 1,

1980 through May 31, 2006, a total of 1,385 women reported endometrial cancer. Medical records including the diagnosis, histologic type, presence of invasion and stage were obtained for 1,105 of these reports. Of these, 669 were classified as cases of invasive adenocarcinoma. The primary reasons for exclusion were that the tumor was non-invasive (n=316), non-epithelial (n=60) or a type of epithelial cancer (n=58) other than adenocarcinoma (e.g., clear cell). Cases of carcinoma in situ were also not included in the analysis. Endometrial carcinoma was further classified as well (grade 1), moderately (grade 2), or poorly (grade 3) differentiated.

Assessment of medical history, anthropometric data and other lifestyle factors—On the 1976 initial NHS questionnaire, we requested information about age, weight and height, smoking status, age at menarche, oral contraceptive use, birth history, cessation of menses, use of postmenopausal hormone therapy, and personal history of other diseases. This information (except height and menarche) has been updated on the biennial follow-up questionnaires. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Postmenopausal hormone (PMH) use and duration of use in months were first asked in 1976. Beginning in 1978 and at each 2-year follow-up, women were asked whether they currently used PMH, number of months used during the 24 months prior to the questionnaire, and the type of PMH.

Statistical Analysis—For each participant, we calculated person-months of follow-up from the date of return of the baseline questionnaire to the date of endometrial cancer (or cancer in situ), hysterectomy, death, or June 1, 2006, whichever came first. We quantified total dairy products (in servings/d) by summing all milk products other than butter since it is only fat and thus unlike other dairy products. Participants were classified according to levels of total dairy consumption. Relative risks (RRs) and 95% confidence intervals (CIs) were calculated using the lowest category of intake as the reference. Absolute zero consumption of dairy did not exist for any of these women because some recipe-based food items, such as sauces or bread, contain small amounts of milk. We used Cox regression models to examine the association between dietary exposures and incidence of endometrial cancer. Hazard ratios were used to estimate relative risk. To test for linear trends across categories, we used the median of each level of total dairy consumption as a continuous variable.

To reduce within-subject variation and best represent long-term effect for diet, we used the cumulative average of dietary intakes from all available dietary questionnaires up to the start of each 2-year follow-up interval (9). For example, the total dairy intake from the 1980 questionnaire was used for the follow-up between 1980 and 1984, the average total dairy intake from the 1980 and 1984 questionnaires were used for the follow-up between 1984 and 1986, the average of the 1980, 1984, and 1986 intakes was used for the follow-up between 1986 and 1990 and so on. In alternative analyses, we also used simple updating (the most recent dietary information before the event) to study short-term effects of dairy on endometrial cancer.

Models were first adjusted for age and two-year follow up cycle. Total energy intake, smoking status, oral contraceptive use, postmenopausal hormone use, age at menopause, parity, age at last birth, age at menarche, hypertension, diabetes, height and body mass index were included in multivariable proportional hazard models (see Table 2 footnote for covariate categories). Age at menopause was defined as the age of the last menstrual period or age at bilateral oophorectomy. Women with unknown menopausal status were considered to be postmenopausal when they reached the age at which 90% of the women reached natural menopause (that is age 56 if a nonsmoker, age 54 if a current smoker) (10). Postmenopausal hormone use, including dose and duration of current use of conjugated estrogen or estrogen plus progestin, were updated biennially.

To assess whether the relationship between total dairy intake and endometrial cancer risk varied across categories of other risk factors, we performed stratified analysis by PMH use (never and past vs. current), smoking status (never vs. past/current) and BMI (BMI<30 vs. BMI≥30kg/m^2). We originally stratified by postmenopausal hormone use in categories of never, past and current, and we then combined never and past together because they were more similar, and both were different from current. We also calculated an interaction term for each dichotomized variable by total dairy intake using the median of each category as a continuous variable and evaluated the Wald statistic. SAS PROC PHREG with SAS version 8.2 was used for all analysis.

RESULTS

From June 1, 1980 through May 31, 2006, we ascertained 669 incident cases of invasive and 264 of pre-invasive adenocarcinomas among the 68,019 women who completed the baseline dietary questionnaire and were eligible for analysis. Among the 669 cases of invasive adenocarcinoma, 337 (50%) were classified as well differentiated, 231 (35%) as moderately differentiated; and 82 (12%) as poorly differentiated, and the remaining 19 (3%) were not-specified.

Milk consumption was fairly stable among the study population over the 26 years of follow-up; mean daily intake was approximately 240 mL (one glass). Characteristics of the population according to cumulative average intake of total dairy consumption data over follow-up are summarized in Table 1. Women who consumed more dairy were less likely to smoke than those who consumed little dairy. The prevalence of other endometrial cancer risk factors was similar across categories.

In age-adjusted analysis, we found a positive association between the cumulative average total dairy consumption and the risk of the endometrial cancer (Table 2). Compared with women who consumed <1 serving of total dairy per week, the relative risk for women who consumed 3+ servings per day was 1.45 (95% CI 1.11–1.90) and the p-value for the linear trend across all categories was 0.001. After multivariate adjustment, the RRs were somewhat attenuated and were no longer statistically significant (3+ vs <1 svg/d: RR 1.26, 95% CI 0.94–1.70, p for trend=0.06)

We also observed a statistically significant positive relation between low-fat milk intake and risk of endometrial cancer in the age-adjusted analysis; the RRs comparing the highest with the lowest categories were 1.41 (95% CI = 1.14–1.76 for trend=0.002). In the multivariate analysis the trend was again attenuated but risk is remained lower in the lowest intake category compared with all others (Table 2). We observed a positive relation between hard cheese intake and risk of endometrial cancer in the age-adjusted analysis; the RR comparing the highest with the lowest category was 1.64 (95% CI = 1.16–2.30 p for trend = 0.06). In the multivariate analysis the trend was attenuated, but a higher risk remained for the highest compared with the lowest category (RR 1.43, 95% CI 1.01–2.04) (Table 2). There was no apparent association between intakes of whole milk, yogurt, butter and endometrial cancer occurrence. We conducted secondary analyses (final models only) on the group of pre-invasive cases. The results for any dairy intake and pre-invasive endometrial cancer did not show any statistically significant difference, although with 264 of pre-invasive cases we had limited power to detect modest associations. The multivariate relative risks of pre-invasive endometrial cancer across categories of cumulatively averaged total dairy consumption compared with < 1 svg/d were: 0.91 (95% CI 0.60–1.30) for 1–1.4 svg/day, 1.22 (0.82–1.82) for 1.5–1.9 svg/day, 0.97 (0.64–1.47) for 2–2.9 svg/day, 1.03 (0.64–1.66) for ≥3 svg/day) (p for trend= 0.91).

To examine timing of dairy consumption in relation to endometrial cancer, we reran analyses using dietary data from the most recent assessment rather than a cumulative average over follow-up. No association between recent total dairy intake and endometrial cancer was observed (RR 1.07, 95% CI 0.80–1.42, for the highest versus lowest intake categories), indicating that long-term intake is more important. We also examined dairy protein and dairy fat to determine whether these components were responsible for the observed association with endometrial cancer, however, no association was observed for either nutrient.

We found that the association between total dairy intake and endometrial cancer was significant only among post-menopausal women. (Women with unknown PMH use were not included.) The relative risk for women who consumed 3 or more servings/day of dairy products, compared to women who consumed <1 servings per day of dairy products, for endometrial cancer, was 1.41 (95% CI 1.01–1.98, p for trend=0.02, P for interaction not significant) (Table 3).

Table 4 summarizes the results of multivariate analyses among postmenopausal women stratified by postmenopausal hormone use (never and past versus current users), smoking status (never versus past and current) and body mass index (<30 versus ≥ 30). As we hypothesized, the association between total dairy intake and risk of endometrial cancer was significant only among women not using postmenopausal hormones. Past and never users of PMH, consuming 3 or more daily servings of dairy were at increased risk for endometrial adenocarcinoma compared to consumers of <1 daily servings. (RR 1.58, 95% CI 1.05–2.36, p for trend 0.003). Among current users of PMH there was no association (RR 1.06, 95% CI 0.57–1.99, p for trend 0.70) (P for interaction 0.054). As its hormone current use that is most related to risk, it would have been interesting to stratify further by postmenopausal hormone type (estrogen alone vs. estrogen-plus-progesterone) but we had too few cases.

There was no suggestion that smoking or BMI modified the association between intake of total dairy and risk of endometrial cancer among postmenopausal women (Table 4). However, since postmenopausal hormone use might confound the results for BMI given that overweight women are less likely to use postmenopausal hormones, we further restricted this analysis to never users only. Though case numbers were low, there was still no clear evidence that BMI modified the association between total dairy intake and endometrial cancer (for 3+ svg/d: RR 1.40, 95% CI 0.59–3.29 for BMI<30; RR 1.21, 95% CI 0.63–2.30 for BMI ≥ 30)..

DISCUSSION

Overall, greater consumption of total dairy intake was associated with a modest increase in risk of invasive adenocarcinoma that was statistically significant only among postmenopausal women, particularly those who were not currently using hormone therapy. An increased risk was observed in the highest category of hard cheese. This is consistent with our previous correlation analysis of international data in which cheese was closely correlated with the incidence of corpus uteri cancer (0.79) and “milk + cheese” was identified as the factor contributing most to an increased incidence of corpus uteri cancer by stepwise multiple-regression-analysis (11).

Few epidemiologic analytical studies have investigated the role of dairy and milk in the etiology of endometrial cancer (12–27). The results from case-control studies examining the relationship between milk and dairy product and risk of endometrial cancer are inconsistent: four case control studies found a positive association (12–15), six case control studies found no association (16–21) and four an inverse association (22–25). Conflicting results were also

reported from the cohort studies: one cohort study in Iowa Women's Health Study (216 cases) examining the association between total dairy intake and endometrial cancer reported no association (26) and another cohort study in Norway (27) (11 cases) found a positive association. According to the WCRF/AICR 2007 report, data for milk and dairy products and endometrial cancer were "were either of too low quality, too inconsistent, or the number of studies too few to allow conclusions to be reached" (28).

The development of endometrial cancer is largely related to prolonged exposure to estrogens without cyclic exposure to progesterone (29). Unopposed estrogens increase mitotic activity in endometrial cells, whereas progesterone reduces the activity (30,31). The identification of factors with even low estrogenic activity is therefore important to prevent this disease. Up to now, diet has been implicated to influence endometrial cancer indirectly as a determinant of obesity, which postmenopausally greatly increases circulating estrogen levels (25). However, estrogen and progesterone also are found in foods from animal origin (32) and dairy products account for 60–80% of the estrogens consumed (33).

Although steroid hormones are lipid-soluble, estradiol and similar compounds are not physiologically active when taken orally, because of first-pass hepatic metabolism. However, dairy products contain estrogens mainly in the form of estrone sulfates (34). Remesar et al. estimated that dairy products could account for over 40% of estrone intake from foods (35). According to Andersson and Skakkebaek (36) water-soluble estrone sulfate has a high oral activity, and once inside the body it can be converted to estrone and estradiol.

Interestingly, authors of another prospective cohort study of milk consumption during pregnancy and infant size at birth in Denmark concluded that data do not support a fat-soluble substance as a growth promoting factor and hypothesized that water-soluble substances in milk increase fetal growth (37). Japanese researchers recently published a paper reporting that the intake of cow's milk significantly increased serum estrone (E1) and progesterone concentrations in humans (38).

Another possible explanation for an association between dairy consumption and endometrial cancer is that consumption of dairy products increases serum levels of insulin-like growth factor (IGF-I) (39–42). IGF-I is positively associated with several malignancies in many, but not all, studies (43–47) although free IGF-I levels were reported to be both inversely (48) and positively associated with endometrial adenocarcinomas (49).

Our study is large with 669 invasive, 264 pre-invasive cases and 1.3 million person-years. The use of repeated measures in the analysis not only accounts for changes in dairy intake over time but also decreases measurement error (50). Also, current milk and dairy intake had high correlations with estimates from four 1-week diet records (7,8). Many biases inherent in case-control studies are avoided by a cohort design with high follow-up rate. Unmeasured confounding is still possible, although we adjusted for many endometrial cancer risk factors.

CONCLUSION

We found that total dairy intake was associated with a modest increased risk of endometrial cancer, particularly among women who were postmenopausal and not currently using postmenopausal hormones. Studies with measured estrogen concentrations are needed to better understand the joint effects of dairy and endogenous estrogens on endometrial cancer risk.

Acknowledgments

Supported by CA87969 from the National Cancer Institute, National Institutes of Health and Breast Cancer Research Foundation.

References

1. Emons G, Gründker C, Hanf V, Hanf V. Are estrogens carcinogens? Zentralbl Gynakol. 2002; 124(12):559–65. [PubMed: 12822069]
2. Persson, I.; Adami, H-O. Endometrial cancer. In: Adami, H-O.; Hunter, D.; Trichopoulos, D., editors. Textbook of cancer epidemiology. New York: Oxford University Press; 2002. p. 359-74.
3. Ganmaa D, Tezuka H, Enkhmaa D, Hoshi K, Sato A. Commercial cows' milk has uterotrophic activity on the uteri of young ovariectomized rats and immature rats. Int J Cancer. 2006; 118(9): 2363–5. [PubMed: 16331633]
4. Ganmaa D, Rich-Edwards J, Pollak M, Nakamoto E, Kleimen K, Tserendolgor U, Willett W, Frazier L. Milk consumption and the prepubertal somatotropic axis. Nutr J. 2007; 6:28. (*co-first authors). [PubMed: 17900364]
5. Stampfer MJ, Willett WC, Speizer FE, Dysert DC, Lipnick R, Rosner B, Hennekens CH. Test of the National Death Index. Am J Epidemiol. 1984; 119(5):837–9. [PubMed: 6720679]
6. Willett, WC. Nutritional Epidemiology. 2. New York: Oxford University Press; 1998. Food Frequency Methods; p. 74-91.
7. Willett WC, Sampson L, Stampfer MJ, Sampson L, Rosner B, Hennekens CH, Speizer FE. Reproducibility and validity of a semiquantitative food frequency questionnaire. Am J Epidemiol. 1985; 122(1):51–6. [PubMed: 4014201]
8. Salvini S, Hunter DJ, Sampson L, Stampfer MJ, Colditz GA, Rosner B, Willett WC. Food-based validation of a dietary questionnaire: the effects of week-to-week variation in food consumption. Int J Epidemiol. 1989; 18(4):858–67. [PubMed: 2621022]
9. Hu FB, Stampfer MJ, Rimm E, Ascherio A, Rosner BA, Spiegelman D, Willett WC. Dietary fat and coronary heart disease: a comparison of approaches for adjusting for total energy intake and modeling repeated dietary measurements. Am J Epidemiol. 1999; 149(6):531–40. [PubMed: 10084242]
10. Colditz GA, Stampfer MJ, Willett WC, Stason WB, Rosner B, Hennekens CH, Speizer FE. Reproducffillity and validity of self-reported menopausal status in a prospective cohort study. American Journal of Epidemiology. 1987; 126(2):319–25. [PubMed: 3605058]
11. Ganmaa D, Sato A. The possible role of female sex hormones in milk from pregnant cows in the development of breast, ovarian and corpus uteri cancers. Medical Hypotheses. 2005; 65:1028–1037. [PubMed: 16125328]
12. Potischman N, Swanson CA, Brinton LA, McAdams M, Barrett RJ, Berman ML, Mortel R, Twiggs LB, Wilbanks GD, Hoover RN. Dietary associations in a case-control study of endometrial cancer. Cancer Causes Control. 1993; 4(3):239–50. [PubMed: 8318640]
13. Petridou E, Kedikoglou S, Koukoulomatis P, Dessypris N, Trichopoulos D. Diet in relation to endometrial cancer risk: a case-control study in Greece. Nutr Cancer. 2002; 44(1):16–22. [PubMed: 12672637]
14. Levi F, Franceschi S, Negri E, La Vecchia C. Dietary factors and the risk of endometrial cancer. Cancer. 1993; 71(11):3575–81. [PubMed: 8490907]
15. Mettlin CJ, Schoenfeld ER, Natarajan N. Patterns of milk consumption and risk of cancer. Nutr Cancer. 1990; 13(1–2):89–99. [PubMed: 2300498]
16. Terry P, Vainio H, Wolk A, Weiderpass E. Dietary factors in relation to endometrial cancer: a nationwide case-control study in Sweden. Nutr Cancer. 2002; 42(1):25–32. [PubMed: 12235647]
17. Jain MG, Howe GR, Rohan TE. Nutritional factors and endometrial cancer in Ontario, Canada. Cancer Control. 2000; 7(3):288–96. [PubMed: 10832115]
18. Littman AJ, Beresford SA, White E. The association of dietary fat and plant foods with endometrial cancer (United States). Cancer Causes Control. 2001; 12 (8):691–702. [PubMed: 11562109]

19. Xu WH, Dai Q, Xiang YB, Zhao GM, Zheng W, Gao YT, Ruan ZX, Cheng JR, Shu XO. Animal food intake and cooking methods in relation to endometrial cancer risk in Shanghai. Br J Cancer. 2006; 95:1568–1592. [PubMed: 17088911]
20. Tzonou A, Lipworth L, Kalandidi A, Trichopoulou A, Gamatsi I, Hsieh CC, Notara V, Trichopoulos D. Dietary factors and the risk of endometrial cancer: a case–control study in Greece. Br J Cancer. 1996; 73:1284–1290. [PubMed: 8630294]
21. Hirose K, Tajima K, Hamajima N, Takezaki T, Inoue M, Kuroishi T, Kuzuya K, Nakamura S, Tokudome S. Subsite (cervix/endometrium)-specific risk and protective factors in uterus cancer. Jpn J Cancer Res. 1996; 87:1001–1009. [PubMed: 8878465]
22. Goodman MT, Hankin JH, Wilkens LR, Lyu LC, McDuffie K, Liu LQ, Kolonel LN. Diet, body size, physical activity, and the risk of endometrial cancer. Cancer Res. 1997; 57 (22):5077–5085. [PubMed: 9371506]
23. McCann SE, Freudenheim JL, Marshall JR, Brasure JR, Swanson MK, Graham S. Diet in the epidemiology of endometrial cancer in western New York. Cancer Causes Control. 2000; 11(10): 965–974. [PubMed: 11142531]
24. Salazar-Martinez E, Lazcano-Ponce E, Sanchez-Zamorano LM, Gonzalez-Lira G, Escudero de los Rios P, Hernandez-Avila M. Dietary factors and endometrial cancer risk. Results of a case-control study in Mexico. Int J Gynecol Cancer. 2005; 15(5):938–45. [PubMed: 16174249]
25. Barbone F, Austin H, Partridge EE. Diet and endometrial cancer: a case-control study. Am J Epidemiol. 1993; 137:393–403. [PubMed: 8460621]
26. Zheng W, Kushi LH, Potter JD, Sellers TA, Doyle TJ, Bostick RM, Folsom AR. Dietary intake of energy and animal foods and endometrial cancer incidence. The Iowa Women's Health Study. Am J Epidemiol. 1995; 142:388–394. [PubMed: 7625403]
27. Ursin G, Bjelke E, Heuch I, Vollset SE. Milk consumption and cancer incidence: a Norwegian prospective study. Br J Cancer. 1990; 61(3):454–9. [PubMed: 2328215]
28. World Cancer Research Fund, American Institute for Cancer Research. Cancers Endometrium. Vol. 7. American Cancer Institute for Cancer Research; Washington, DC: 2007. Food, nutrition, physical activity, and cancer risk; p. 302
29. De Vivo I, Huggins GS, Hankinson SE, Lescault PJ, Boezen M, Colditz GA, Hunter DJ. A functional polymorphism in the promoter of the progesterone receptor gene associated with endometrial cancer risk. Proc Natl Acad Sci USA. 2002; 99(19):12263–8. [PubMed: 12218173]
30. Ehrlich CE, Young PC, Cleary RE. Cytoplasmic progesterone and estradiol receptors in normal, hyperplastic, and carcinomatous endometria: therapeutic implications. Am J Obstet Gynecol. 1981; 141(5):539–46. [PubMed: 6457531]
31. Persson I, Adami H, Bergkvist L, Lindgren A, Pettersson B, Hoover R, Schairer C. Risk of endometrial cancer after treatment with oestrogens alone or in conjunction with progestogens: results of a prospective study. BMJ. 1989; 298(6667):147–51. [PubMed: 2538173]
32. Daxenberger A, Ibarreta D, Meyer HH. Possible health impact of animal oestrogens in food. Hum Reprod Update. 2001; 7(3):340–55. [PubMed: 11392381]
33. Hartmann S, Lacorn M, Steinhart H. Natural occurrence of steroid hormones in food. Food Chem. 1998; 62:7–20.
34. Hamon M, Fleet IR, Heap RBM, Fleet IR, Heap RB. Comparison of oestrone sulphate concentrations in mammary secretions during lactogenesis and lactation in dairy ruminants. J Dairy Res. 1990; 57:419–22. [PubMed: 2169489]
35. Remesar X, Tang V, Ferrer E, Torregrosa C, Virgili J, Masanés RM, Fernández-López JA, Alemany M. Estrone in food: a factor influencing the development of obesity? Eur J Nutr. 1999; 38:247–53. [PubMed: 10654162]
36. Andersson AM, Skakkebaek NE. Exposure to exogenous estrogens in food: possible impact on human development and health. Eur J Endocrinol. 1999; 140(6):477–85. [PubMed: 10366402]
37. Olsen SF, Halldorsson TI, Willett WC, Knudsen VK, Gillman MW, Mikkelsen TB, Olsen J. NUTRIX Consortium. Milk consumption during pregnancy is associated with increased infant size at birth: prospective cohort study. Am J Clin Nutr. 2007; 86(4):1104–10. [PubMed: 17921389]

38. Maruyama K, Oshima T, Ohyama K. Exposure to exogenous estrogen through intake of commercial milk produced from pregnant cows. Pediatrics International. 2010; 52:33–8. [PubMed: 19496976]
39. Holmes MD, Pollak MN, Willett WC, Hankinson SE. Dietary correlates of plasma insulin-like growth factor-I and insulin-like growth factor binding protein-3 concentrations. Cancer Epidemiol Biomarkers Prev. 2002; 11:852–861. [PubMed: 12223429]
40. Morimoto LM, Polly A, Newcomb PA, White E, Bigler J, Potter JD. Variation in plasma insulin-like growth factor-1 and insulin-like growth factor binding protein-3: personal and lifestyle factors. Cancer Causes Control. 2005; 16:917–927. [PubMed: 16132801]
41. Norat T, Dossus L, Rinaldi S, Overvad K, Grønbaek H, Tjønneland A, Olsen A, Clavel-Chapelon F, Boutron-Ruault MC, Boeing H, Lahmann PH, Linseisen J, et al. Diet, serum insulin-like growth factor-I and IGF-binding protein-3 in European women. Eur J Clin Nutr. 2007; 61:91–98. [PubMed: 16900085]
42. Crowe FL, Key TJ, Allen NE, Appleby PN, Roddam A, Overvad K, Grønbaek H, Tjønneland A, Halkjaer J, Dossus L, Boeing H, Kröger J, et al. The association between diet and serum concentrations of IGF-I, IGFBP-1, IGFBP-2, and IGFBP-3 in the European Prospective Investigation into cancer and nutrition. Cancer Epidemiol Biomarkers Prev. 2009; 18(5):1333–1340. [PubMed: 19423514]
43. Renehan AG, Zwahlen M, Minder C, O'Dwyer ST, Shalet SM, Egger M. Insulin-like growth factor (IGF)-I, IGF binding protein-3, and cancer risk: systematic review and meta-regression analysis. Lancet. 2004; 24:363(9418):1346–53. [PubMed: 15110491]
44. Baglietto L, English DR, Hopper JL, Morris HA, Tilley WD, Giles GG. Circulating insulin-like growth factor-I and binding protein-3 and the risk of breast cancer. Cancer Epidemiol Biomarkers Prev. 2007; 16(4):763–8. [PubMed: 17416768]
45. Roddam AW, Allen NE, Appleby P, Key TJ, Ferrucci L, Carter HB, Metter EJ, Chen C, Weiss NS, Fitzpatrick A, Hsing AW, Lacey JV Jr, et al. Insulin-like growth factors, their binding proteins, and prostate cancer risk: analysis of individual patient data from 12 prospective studies. Ann Intern Med. 2008; 7;149(7):461–71. W83–8.
46. Wu MH, Chou YC, Chou WY, Hsu GC, Chu CH, Yu CP, Yu JC, Sun CA. Relationships between critical period of estrogen exposure and circulating levels of insulin-like growth factor-I (IGF-I) in breast cancer: evidence from a case-control study. Int J Cancer. 2010; 15;126(2):508–14.
47. Key TJ, Appleby PN, Reeves GK, Roddam AW. The Endogenous Hormones and Breast Cancer Collaborative Group. Insulin-like growth factor 1 (IGF1), IGF binding protein 3 (IGFBP3), and breast cancer risk: pooled individual data analysis of 17 prospective studies. Lancet Oncol. 2010; 11(6):530–42. [PubMed: 20472501]
48. Gunter MJ, Hoover DR, Yu H, Wassertheil-Smoller S, Rohan TE, Manson JE, Li J, Ho GY, Xue X, Anderson GL, Kaplan RC, Harris TG, et al. A prospective evaluation of insulin and insulin-like growth factors-1as risk factors for endometrial cancer. Cancer Epidemiol Biomarkers Prev. 2008; 17(4):921–9. [PubMed: 18398032]
49. Oh JC, Wu W, Tortolero-Luna G, Broaddus R, Gershenson DM, Burke TW, Schmandt R, Lu KH. Increased plasma levels of insulin-like growth factor 2 and insulin-like growth factor binding protein 3 are associated with endometrial cancer risk. Cancer Epidemiol Biomarkers Prev. 2004; 13(5):748–52. [PubMed: 15159305]
50. Willett WC, Sampson L, Browne ML, Stampfer MJ, Rosner B, Hennekens CH, Speizer FE. The use of a self-administered questionnaire to assess diet four years in the past. Am J Epidemiol. 1988; 127:188–199. [PubMed: 3337073]

Table 1

Baseline characteristics by cumulative average intake of total dairy among participants the Nurses' Health Study

	Total Dairy Intake				
	<1svg/d	**1–1.49svg/d**	**1.5–1.99 svg/d**	**2–2.99 svg/d**	**3+ svg/d**
Age	54.2	55.5	56.5	57.0	55.7
Age at menarche (yr)	12.5	12.5	12.4	12.5	12.5
Height (in)	64.2	64.4	64.5	64.6	64.7
Parity*	3.2	3.2	3.2	3.2	3.3
Age at menopause	49.7	50.0	50.1	50.2	50.2
BMI (continuous)	25.4	25.6	25.8	25.8	25.7
BMI≥30	15.7%	16.2%	17.3%	17.7%	17.4%
Ever used oral contraceptives	48%	50%	51%	51%	48%
Post-menopausal	62%	62%	62%	62%	62%
Past PMH use	15%	16%	16%	16%	15%
Current PMH use	13%	15%	15%	16%	15%
Ever smoked	62%	59%	56%	55%	53%
History of hypertension	29%	28%	28%	27%	26%
History of diabetes	4.4%	4.1%	4.3%	4.6%	4.7%

Values that are not percentages are means unless otherwise indicated. BMI: body mass index;

Age at menopause and postmenopausal hormone use were calculated among postmenopausal women only.

Table 2

Cumulative average intake of dairy and risk of endometrial cancer, 1980–2006[†]

			Frequency of intakes			P for trend
Total dairy	(<1 svg/d)	(1–1.4 svg/d)	(1.5–1.9 svg/d)	(2–2.9 svg/d)	(3+ svg/d)	
# of cases	89	112	143	188	137	
Person-years (yr ×10^3)	229	269	256	327	218	
Minimal model, RR (95% CI)[*]	1.00	0.99(0.75–1.31)	1.26(0.96–1.64)	1.25(0.97–1.61)	1.45(1.11–1.90)	0.001
Multivariate model, RR (95% CI)[†]	1.00	0.94(0.71–1.25)	1.14(0.87–1.49)	1.10(0.84–1.44)	1.26(0.94–1.70)	0.06
Low-fat milk	<1 svg/w	1–1.9 svg/w	2–4.9 svg/w	5–6.9 svg/w	1+ svg/d	
# of cases[‡]	131	68	151	91	224	
Person-years (yr ×10^3)	319	255	165	240	281	
Minimal model, RR (95% CI)[*]	1.00	1.30(0.97–1.75)	1.14(0.90–1.45)	1.40(1.06–1.83)	1.41(1.14–1.76)	0.002
Multivariate model, RR (95% CI)[†]	1.00	1.23(0.91–1.65)	1.03(0.81–1.31)	1.21(0.92–1.58)	1.18(0.94–1.47)	0.19
Whole milk						
# of cases	475	62	83	48		
Person-years (yr ×10^3)	905	113	143	121		
Minimal model, RR (95% CI)[*]	1.00	0.99(0.76–1.29)	1.09(0.86–1.38)	0.92 (0.68–1.25)		0.85
Multivariate model, RR (95% CI)[†]	1.00	1.02(0.78–1.33)	1.16(0.91–1.46)	1.02 (0.75–1.38)		0.60
Yogurt						
# of cases	519	103	33	10		
Person-years (yr ×10^3)	946	179	138	24		
Minimal model, RR (95% CI)[*]	1.00	1.00(0.81–1.24)	0.84(0.65–1.08)	0.86 (0.46–1.60)		0.22
Multivariate model, RR (95% CI)[†]	1.00	0.95(0.77–1.18)	0.81(0.63–1.05)	0.86 (0.46–1.61)		0.14
Hard cheese						
# of cases	84	142	331	54	56	
Person-years (yr ×10^3)	189	268	610	134	98	
Minimal model, RR (95% CI)[*]	1.00	1.14(0.87–1.49)	1.19(0.94–1.51)	1.01(0.72–1.42)	1.64(1.16–2.30)	0.06
Multivariate model, RR (95% CI)[†]	1.00	1.09(0.83–1.43)	1.08(0.84–1.37)	0.89(0.63–1.27)	1.43(1.01–2.04)	0.38

[*] Stratified by age and period

[†]Adjust for total energy (continuous), smoking [never(reference), past, current], oral contraceptive use [never (reference), < 3 years, 3–5 years, > 5 years], postmenopausal hormone use [premenopausal, postmenopausal never(reference), past, current E only, current E+P], age at menopause [pre/unknown menopause, <45 yr, 45–46 yr, 47–48 yr (reference), 49–50 yr, 51–52 yr, 53+ yr] parity [nulliparous (reference), 1–2 & age at last birth<30, 1–2 & age at last birth>=30, 3–4 & age at last birth<30, 3–4 & age at last birth>=30, 5+], age at menarche [< 12, 12 (reference), > 12], hypertension (yes, no), diabetes (yes, no), BMI (continuous), height (continuous).

[‡]Cases # varies due to missing variables

Int J Cancer. Author manuscript; available in PMC 2013 June 01.

Table 3

Cumulative average intake of dairy and risk of endometrial cancer stratified by menopausal status, 1980–2006 [*†]

	Frequency intake of total dairy					p_{trend}	$p_{Interaction}$
Total Dairy	<1 svg/d	1–1.4 svg/d	1.5–1.9 svg/d	2–2.9 svg/d	3+ svg/d		
Premenopausal							
# of cases	16	16	17	24	20		
RR (95% CI)	1.00	0.83(0.41–1.67)	0.87(0.43–1.76)	0.94(0.48–1.84)	0.95(0.45–1.99)	0.92	
Postmenopausal							
# of cases	68	92	118	156	111		
RR (95% CI)	1.00	1.01(0.73–1.38)	1.22(0.90–1.66)	1.20(0.89–1.63)	1.41(1.01–1.98)	0.02	0.95

[*] Women with dubious menopausal status or unknown PMH use status were not included.

[†] Adjusted for total energy (continuous), smoking [never(reference), past, current], oral contraceptive use [never (reference), < 3 years, 3–5 years, > 5 years], postmenopausal hormone use [premenopausal, postmenopausal never(reference), past, current E only, current E+P], age at menopause [pre/unknown menpause, <45 yr, 45–46 yr, 47–48 yr (reference), 49–50 yr, 51–52 yr, 53+ yr] parity [nulliparous (reference), 1–2 & age at last birth<30, 1–2 & age at last birth>=30, 3–4 & age at last birth<30, 3–4 & age at last birth>=30, 5+ & age at last birth<30, 5+], age at menarche [< 12, 12 (reference), > 12], hypertension (yes, no), diabetes (yes, no), BMI (continuous), height (continuous).

Table 4

Cumulative average intake of total dairy and risk of endometrial cancer among postmenopausal women stratified by PMH use, smoking, and BMI, 1980–2006[†]

	Frequency of intakes					p_{trend}	$p_{Interaction}$
	<1 svg/d	1–1.4 svg/d	1.5–1.9 svg/d	2–2.9 svg/d	3+ svg/d		
By PMH use [*]							
Never/past users							
# of cases	47	51	82	110	81		
RR (95% CI)	1.00	0.84 (0.56–1.25)	1.27(0.88–1.83)	1.30(0.90–1.86)	1.58(1.05–2.36)	0.003	
Current users							
# of cases	21	41	36	46	30		
RR (95% CI)	1.00	1.32 (0.78–2.25)	1.11(0.64–1.93)	1.02(0.59–1.76)	1.06(0.57–1.99)	0.70	0.054
By smoking							
Never smoke							
# of cases	31	42	66	68	62		
RR (95% CI)	1.00	0.98 (0.61–1.57)	1.40(0.90–2.18)	1.05(0.67–1.64)	1.52(0.94–2.46)	0.10	
Ever smoke							
# of cases	37	50	52	88	49		
RR (95% CI)	1.00	1.04 (0.68–1.60)	1.05(0.68–1.63)	1.35(0.90–2.04)	1.32(0.82–2.12)	0.12	0.94
By BMI							
BMI<30							
# of cases	39	64	77	99	63		
RR (95% CI)	1.00	1.21(0.81–1.81)	1.42(0.96–2.11)	1.40(0.95–2.07)	1.44(0.93–2.24)	0.14	
BMI≥30							
# of cases	29	28	41	57	48		
RR (95% CI)	1.00	0.78 (0.46–1.31)	0.99(0.61–1.62)	1.02(0.63–1.64)	1.45(0.85–2.46)	0.09	0.48

[*] Women with uncertain menopausal status or unknown PMH use status were not included.

[†] Adjusted for the same covariates as in Table 3, except for the stratification factors themselves:

- **a.** within the stratum of never/past users, PMH was adjusted (past vs. never); in stratum of current users, PMH was also adjusted (E+P vs. E only).
- **b.** within the strata of never or ever smokers, smoking was not adjusted.
- **c.** within the strata of BMI>=30/<30, continuous BMI was adjusted.