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Dairy Products and Cancer Risk in a Northern Sweden Population

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ABSTRACT

The role of dairy products in cancer is unclear. We assessed consumption of fermented milk, non-fermented milk, cheese, and butter, estimated from semi-quantitative food frequency questionnaires, in relation to prospective risk of breast, prostate, colorectal, smoking-, and obesity-related cancers in 101,235 subjects, including 12,552 cancer cases, in the population-based Northern Sweden Health and Disease Study. Most analyses ($n = 20$) rendered null results. In men, we observed an increased prostate cancer risk among high-consumers of cheese (hazard ratio (HR) for highest vs. lowest quintile (Q5–Q1), 1.11; 95% CI, 0.97–1.27; $p^{\text{trend}} = 0.013$). In women, high-consumers of cheese had a decreased risk of overall cancer (HR Q5–Q1, 0.95; 95% CI, 0.88–1.04; $p^{\text{trend}} = 0.039$), smoking-related (HR Q5–Q1, 0.84; 95% CI, 0.72–0.97; $p^{\text{trend}} \leq 0.001$), and colorectal cancers (HR Q5–Q1, 0.82; 95% CI, 0.63–1.07; $p^{\text{trend}} = 0.048$). Butter yielded a weak decreased obesity-related cancer risk in women (HR Q5–Q1, 0.91; 95% CI, 0.81–1.02; $p^{\text{trend}} = 0.049$). Fermented milk yielded HRs below zero in women, but with no clear linear associations. In conclusion, this study does not support any major adverse or beneficial effects of fermented milk, non-fermented milk, cheese, and butter in the diet from a cancer risk perspective.

ARTICLE HISTORY

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Introduction

Cancer is a major public health threat with an expected increase in morbidity worldwide paralleling welfare development and aging populations. It is estimated that more than 20 million new cancer patients will be diagnosed every year until 2030 (1). Consequently, changes in even modest risk factors can be expected to have a substantial impact on overall incidence, with implications for public health. Nutrition plays a key role in cancer development and growth (2). Many cancers may be prevented by dietary modifications, such as avoiding red meat and increasing consumption of plant-based food (3). Lacto-vegetarians and others who do not want to substitute red meat solely with plant-based protein sources, such as beans, may find dairy products an attractive alternative. In order to evaluate the potential impact of this food regime on cancer risk, the role of dairy products in cancer development needs further elucidation.

Dairy products, primarily based on cow's milk, are widely consumed worldwide and represent a wide array

of foods and beverages differing in proportions of proteins, fats, minerals, other bioactive compounds, and microbiota. From a cancer perspective, some of these compounds are of specific interest, including insulin-like growth factor (IGF), calcium, lactoferrin, vitamin D, lactic acid producing bacteria, and dairy lipids (4).

Excluding indirect contribution to cancer development by overeating (5), the IGF raising effect of consuming dairy products (6) has been highlighted as a main adverse risk factor for cancer development in general (4), and prostate cancer development in specific (7). For breast and colorectal cancer, a high calcium intake seems beneficial (8, 9), while in lung cancer it is neutral (10), and in prostate cancer calcium restriction is preferable (11). In animal as well as clinical studies, lactoferrin has been demonstrated to suppress tumor growth (12), and vitamin D to act as an antitumor agent by counteracting mitogenesis (13). This is valid both for naturally occurring vitamin D, and variants in supplemented dairy products (14).

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Lactic acid producing bacteria, plentifully available in cheeses and fermented dairy products, impact the gut microbiome, increases bioavailability of vitamin D and lactoferrin and balance bowel inflammation, which could have positive implications for cancer prevention (4). Furthermore, dairy lipids and fatty acids, such as linoleic acid, butyric acid, phospholipids, and sphingolipids, are likely beneficial from a cancer health perspective (15). Given the potentially contradictory effects of various components of dairy products in carcinogenesis, a clear hypothesis for the relationship between dairy intake and cancer risk cannot be made.

Consumption of dairy products has been evaluated in relation to cancer risk in cohort studies (16–21) and cohort meta-analyses (10,22–30). Comprehensive summaries of the evidence to date are regularly published by the World Cancer Research Fund (WCRF), as part of the Continuous Update Project. In short, according to the most recent WCRF report, published in 2018, dairy products represent a food group where “evidence is divergent between cancer sites” (4). The report highlights beneficial health effects on colorectal cancer (probable), and premenopausal breast cancer (suggestive), and adverse health effects on prostate cancer (suggestive) (4). In addition, adverse health effects of dairy consumption in gastric, (22), hepatocellular (21), renal (26), and ovarian cancer (30) have been suggested, as well as potential beneficial effects of fermented dairy products in bladder and esophageal cancer (26). Cancer sites with inconclusive results include endometrial (23), lung (10), pancreatic (25), breast, laryngeal, lymphoma, oral, and pharyngeal cancers (4,26). Interpretation of the epidemiological studies to date is hindered by different methods of categorizing dairy products, with some studies merging some or all dairy products (17,18), and others categorizing dairy products into common staple groups, such as non-fermented milk, fermented milk, and cheese (16,19–21). Categorization according to fat content is also common, whereas there is a knowledge gap consisting of a relatively low number of studies addressing butter consumption in relation to cancer risk and studies in populations with a high consumption of non-fermented dairy products. In Sweden, a majority of the population, >90%, is lactose tolerant (31), which allows for a high consumption of non-fermented dairy products. The per capita milk consumption scores within the top five worldwide (32), and the distribution of dairy intake is wide.

The aim of this study was to investigate intake of four dairy product categories in relation to the risk of incident cancer, including specific cancer sites and

smoking- and obesity-related cancer, in a population with a high tolerance to non-fermented dairy products. We used prospectively collected data from 105,891 subjects, including 12,552 cancer cases, in population-based cohorts in northern Sweden.

Materials and Methods

Study Design and Study Subjects

This prospective cohort study is derived from the Northern Sweden Diet database (NSDD; <https://www.umu.se/en/biobank-research-unit/research/nsdd—northern-sweden-diet-database/basic-information/>), which contains baseline characteristics and refined dietary data from the Northern Sweden Health and Disease Study cohorts (NSHDS), described in detail elsewhere (33). A detailed variable list is available at the homepage (List of variables and DTA for NSDD, <https://www.umu.se/globalassets/organisation/fakulteter/medfak/enheten-for-biobanksforskning/uttag/list-of-variables-nsdd-190325.docx>). Subjects are recruited through two cohorts initiated in the mid-1980s, the Västerbotten Intervention Programme (VIP), and the Northern Sweden Monitoring of Trends and Determinants in Cardiovascular disease (MONICA) project. VIP focuses on Västerbotten, the second northernmost county of Sweden. Inhabitants turning 40-, 50-, and 60 years of age are invited to their primary health care center for a health examination. Until 1995, also 30-year-olds were invited. MONICA (<http://www.org.umu.se/monica>) includes inhabitants from the entire arctic region of Sweden, that is, the two northernmost counties, Västerbotten and Norrbotten. Since 1986, a random sample of 2,000–2,500 people aged 25–75 years, are invited to a sampling occasion every fourth or fifth year.

The structure of the health screenings in VIP and MONICA are very similar, including answering an extensive questionnaire on health and living conditions, along with a food frequency questionnaire (FFQ). Height, weight, blood pressures, blood lipid profile, and blood glucose levels are measured after least 4 h fasting, generally 8 h, and glucose is measured again after an oral glucose load (34). Optionally, and in most cases, subjects also provide a blood sample for biobank research. Over time, the participation rates were 48–67% in VIP and 63–81% in MONICA. The seemingly lower participation rate in VIP reflects that the nominator represents the total eligible population but all were not invited for financial and time reasons (34). Cancer rates in NSHDS are very similar to those of the general population in arctic Sweden

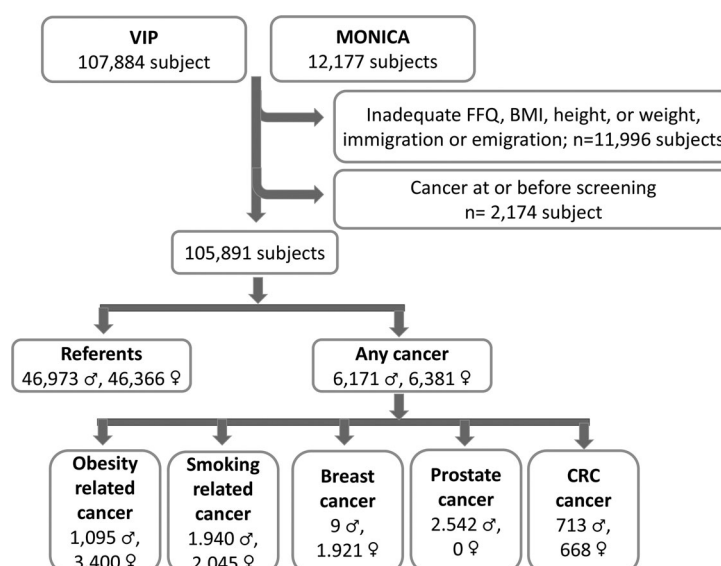


Figure 1. Flowchart from inclusion of the VIP and MONICA subjects to final cancer case groups.

(35), and there is limited evidence of selection bias regarding income, age, and unemployment (36,37), indicating a representative population-based cohort.

For the present study, we selected the first sampling event in NSDD during the period 1986 (January 1) to 2016 (December 31), resulting in 120,061 potential subjects.

Observations were based on the first sampling occasion for subjects with repeated measures and excluded if: i) the food intake recording was incomplete, that is, $\geq 10\%$ missing data and/or a missing portion indication, extreme food intake levels (highest and lowest 1%) (38), and extreme energy intakes (lowest 1% and $>5,000$ kCal) and ii) implausible height (<130 or >210 cm) or weight (<35 kg) values, or BMI < 15.0 . We also excluded subjects who had immigrated or emigrated during the follow-up period. The final study group comprised 105,891 subjects (49.8% women). The flowchart for participant selection is shown in Fig. 1.

Ethical Approval

The regional Ethical Review Board of Northern Sweden, Umeå, has approved the study protocol and data handling procedures of the study (Dnr 2013/332/31). All study subjects provided written informed consent and the study was conducted in accordance with the Declaration of Helsinki and The General Data Protection Regulation (GDPR) legislation.

Dietary Assessment

When completing the FFQ, the subjects were asked to describe their dietary habits over the latest year. Two

FFQ versions have been used during the study period; one with 84 items (long version, 37% of the subjects) and one with 64–66 items (short version, 63% of the subjects). The main difference between the FFQ versions is the aggregation of some food items in the shorter version. Questions on dairy products were identical in the long and the short version. Intake frequencies were assessed by nine fixed options, ranging from never to four or more times per day. Portion sizes were described by letting subjects select one of four color photographs of plates with increasing amounts of staple foods, that is, potato/rice/pasta, meat/fish, and vegetables. These estimates, together with sex and age specific standard intakes of other foods and food compositions provided by the National Food Agency, Sweden (www.livsmedelsverket.se/), were transformed into daily intakes of energy and nutrients, according to methods described elsewhere (39). Consumption (servings/day) of non-fermented milk was defined through merging three FFQ food items describing non-fermented milk with different fat content (0.5%, 1.5%, and 3%). Consumption of fermented milk was defined through two FFQ items on fermented milk (high and low fat). Consumption of cheese was specified through two FFQ items on cheese with different fat content (10–17% or 28%). Consumption of butter was defined through three FFQ items on Bregott (a butter-based spread), butter as spread, and butter for cooking. The FFQ has been validated by repeated 24-h dietary recalls and biological markers (39–42), demonstrating similar validity and reproducibility to other prospective cohort studies.

Identification of Cancer Cases

Information on all cancer diagnoses in the eligible cohort, that is, subjects with adequate dietary data in the NSDD, was obtained by linkage to the Swedish Cancer Register at the National Board of Health and Welfare in Sweden (www.socialstyrelsen.se/register), using personal identification numbers. In addition to all first malignancies, excluding non-melanoma skin cancer, the following specific cancer types were identified using ICD10 codes: breast (C50), prostate (C61), and colorectal (C18-C20.9) cancer. Smoking- and obesity-related cancers were defined according to the International Agency for Research on Cancer as cancer of the lip/oral cavity/pharynx (C00-C14), esophagus (C15), gastric (C16), colorectum (C18-C20.9), liver/intrahepatic bile ducts (C22), pancreas (C25), larynx/trachea/bronchus/lung (C32-C34), cervix (C53, D06), kidney (C64), bladder (C67), and bone-marrow (acute and chronic myeloid leukemia, C91-95 and D46, excluding C91.4) (43). Obesity-related cancers were defined as cancer of the esophagus (C15), colorectum (C18-C20.9), liver (C22), gallbladder (C23), pancreas (C25), ovary (C56), endometrium (C54.1), kidney (C64), and breast (C50) (post-menopausal, approximated as breast cancers diagnosed after the age of 55 years) (44). The first incident cancer diagnosis was considered, resulting in 12,552 cancer cases (50.8% women) identified and a reference group of 93,339 subjects (49.7% women) remained (Fig. 1).

Assessment of Covariates

BMI (body weight/height²) was calculated from body weight (kg) and height (m) measured in subjects wearing light clothes and no shoes. Information on civil status, smoking, highest level of education, physical activity in leisure time, daily intakes of alcohol, fruits and vegetables, and total energy was collected from the questionnaires. Smoking was categorized as never used, past daily or occasional use, or present daily or occasional use. For civil status subjects were categorized into four levels (single, married/cohabiting, widower, and divorced), for education four levels ranging from primary school or less to academic post-secondary education, and for recreational physical activity, five levels reflecting inactive to exercising in workout clothes more than three times a week were used. For the dietary variables, subjects were classified into quintiles (by gender and 10-year age group) based on the distribution of reported intake (energy, alcohol, and fruit and vegetables) among consumers in the study cohort.

Data Processing and Statistical Analyses

Subjects were categorized as nonconsumers (those reporting null intake of a dairy food item) or consumers (those reporting any intake). Categorical measures are presented as proportions (%) and continuous measures as means, adjusted for sex (if not stratified for sex), age, and screening year, and standard deviations (SD) or 95% confidence limits (CI). Differences between group numbers/means were not tested if the difference was interpreted as biologically irrelevant and the large groups likely induced a statistically significance. When tests were applied, distributions of group numbers were tested with a Chi²-test and differences between group means with ANOVA in general linear model multiple regression.

After nonconsumers had been placed in a “nonconsumer” category, consumers were classified into quintiles based on the distribution of their reported intake/day of each targeted dairy food item. Ranking was done in sex and 10-year age strata. Thus, totally six categories were compared.

Cox proportional hazards regression and hazard ratios (HR) were calculated to estimate the risk of developing cancer endpoints during the follow-up period for the categories of dairy product intake, and calculated separately for men and women. Time (months) between the health screening and diagnosis or end of the study period (December 31, 2016), which ever occurred first, was used as the time scale. The group with the lowest reported intake was the reference group. The proportional hazards assumption was evaluated by Schoenfeld residuals and was not violated. Basic models included, screening year and dairy product category. Covariates were selected a priori for multivariable analysis based on their known associations with cancer risk and consumption of dairy products. Adjusted models included the covariates from the basic models as well as BMI, civil status, education level, physical activity in leisure time, smoking status, recruitment cohort (VIP or MONICA), and quintiles of fruit-and vegetables, alcohol, and energy intake. Energy-adjustment of the dietary variables, using residuals, did not affect the results, and were therefore not used. To examine linear trends in risk, we excluded nonconsumers and used the ordinal number of each dairy intake quintile as a continuous variable in the analyses.

The following sensitivity analyses were done for the HR estimates: i) exclusion of cases with a diagnosis within the first year after data collection and ii) mutual adjustment for intake of other dairy or related complementary products, that is, margarin for butter

Table 1. Baseline characteristics of the study subjects.

Characteristics	Referents <i>n</i> = 93,339	Any cancer <i>n</i> = 12,552	<i>P</i> -value
Male/female (%)	50.3/49.7	49.2/50.8	0.015
Age, years (mean (SD))	45.9 (9.4)	54.9 (8.3)	<0.001
University level (%)	29.5	23.8	<0.001
Married (%)	80.2	80.7	<0.001
Smoking (%)			<0.001
Present	19.6	22.2	
Past	28.7	34.5	
Never	51.7	43.3	
Snus (Swedish moist snuff) (%)			<0.001
Present	18.2	13.7	
Past	11.6	10.0	
Never	70.2	76.3	
Inactive at leisure time (%)	38.7	46.2	<0.001
BMI (kg/m ²)	26.0 (4.3)	26.0 (4.1)	0.644
Total cholesterol ^a (mmol/L)	5.5 (1.2)	5.4 (1.2)	<0.001
Triglycerides ^a (mmol/L)	1.4 (0.9)	1.4 (0.8)	0.231
Fasting blood sugar (mmol/L)	5.4 (0.9)	5.4 (1.2)	0.376
Systolic blood pressure (mmHg)	126 (17)	126 (19)	0.315
Diastolic blood pressure (mmHg)	79 (11)	78 (11)	0.010
Total fat intake (E%)	35.3 (7.0)	35.1 (6.4)	0.037
Saturated fat intake (E%)	14.8 (3.7)	14.7 (3.5)	0.045
Protein intake (E%)	14.7 (2.3)	14.7 (2.2)	0.922
Carbohydrate intake (E%)	47.5 (7.4)	47.7 (6.7)	0.001
Sucrose (E%)	6.4 (3.0)	6.5 (3.2)	0.001
Energy (kCal/day)	1,741 (592)	1,756 (580)	0.004
Alcohol (g/day)	4.12 (4.82)	4.25 (4.98)	0.004
Fruit and vegetables (servings/day)	2.98 (1.96)	2.95 (1.97)	0.072

Data are presented as sex, age, and screening year adjusted means with standard deviations (SD), or as valid percent within the group.

^aThese means were also adjusted for analysis before or after September 1, 2009, when the laboratory method changed.

estimates, which was done to account for positive or negative influences from other foods when low levels were consumed of the test food.

Data processing and statistical analyses were performed with SPSS version 25 (IBM; SPSS Software). All tests were two-sided, and $P < 0.05$ was considered statistically significant.

Results

Characteristics of Study Subjects

Of the 108,065 subjects with adequate information in the NSDD, 12,552 incident cancer cases were identified, that is, cases diagnosed after data collection during a mean follow-up of 19.9 years. The breakdown by cancer type is shown in Fig. 1. The mean follow-up time for cases from data collection to diagnosis was 11.2 years (SD 6.8).

Baseline characteristics of the study population are shown in Table 1. In general, cancer cases were older at recruitment, had a lower education level, were more likely to be active smokers, have an inactive leisure time, and abstain from Swedish moist snuff. Several other baseline characteristics showed statistically significant, but small, differences between cancer

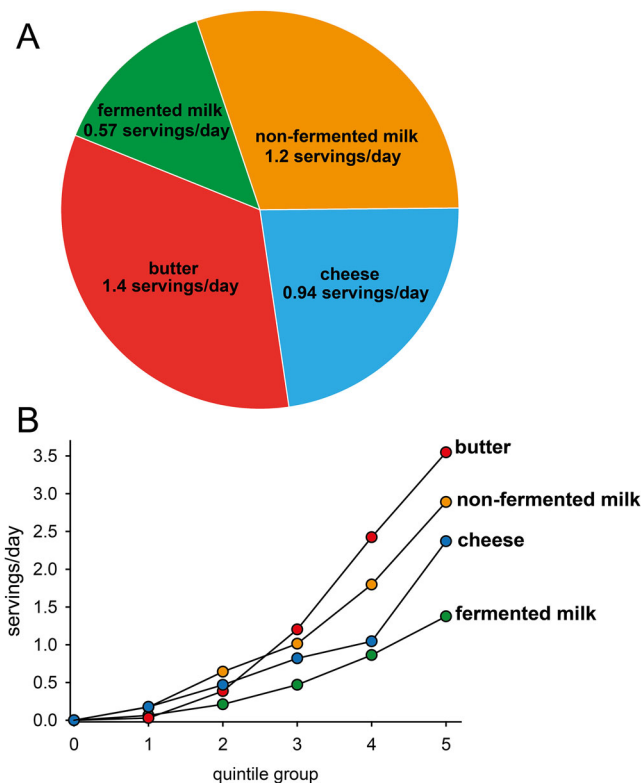


Figure 2. A: Distribution, and mean daily intake, of the four dairy product categories among total dairy intake in the study population. B: Sex standardized mean daily intake in the four dairy product categories by quintile categories.

cases and the referent group. Reported alcohol intake did not differ significantly between cases and referents (Table 1).

Consumption patterns of dairy products and the distribution of quintiles are shown in Figs. 2A,B. In the study population, non-fermented milk contributed to 30% of total dairy (mean, 1.2 servings/day), fermented milk contributed to 14% (mean, 0.57 servings/day), butter to 33% (mean 1.4 servings/day), and cheese to 23% (mean 0.94 servings/day) of the total dairy intake (Fig. 2A). The quintiles of non-fermented milk ranged from a mean of 0.2 servings/day in the lowest to a mean of 2.9 servings per day in the highest. Corresponding figures for other dairy products were: fermented milk (mean Q1–Q5, 0.064–1.4 servings/day), butter (mean Q1–Q5, 0.030–3.5 servings/day), and cheese (mean Q1–Q5, 0.18–2.4 servings/day) (Fig. 2B).

Dairy Intake and Incident Cancer in Men and Women, Respectively

Sex-stratified associations between dairy products (i.e., non-fermented milk, fermented milk, cheese, and butter) and cancer risk, are presented in Tables 2, 3, 4, 5,

Table 2. Hazard ratios (95% CIs) for intakes of dairy products and cancer of any type calculated from ^abasic and ^badjusted Cox proportional hazard models.

	Men			Women		
	Cases	Basic ^a HR (95% CI)	Adjusted ^b HR (95% CI)	Cases	Basic ^a HR (95% CI)	Adjusted ^b HR (95% CI)
All cancer types						
Non-fermented milk						
Q0	282	1.07 (0.94; 1.22)	1.06 (0.93; 1.21)	354	1.15 (1.02; 1.30)	1.15 (1.02; 1.29)
Q1 (reference)	1155	1.00	1.00	1100	1.00	1.00
Q2	1001	0.98 (0.90; 1.06)	0.98 (0.90; 1.07)	1028	1.04 (0.96; 1.13)	1.04 (0.96; 1.14)
Q3	1353	1.04 (0.96; 1.12)	1.02 (0.94; 1.11)	1525	1.10 (1.02; 1.19)	1.11 (1.03; 1.20)
Q4	1245	0.99 (0.92; 1.08)	0.99 (0.91; 1.08)	1055	1.03 (0.95; 1.12)	1.06 (0.97; 1.15)
Q5	1135	1.01 (0.93; 1.10)	1.02 (0.93; 1.11)	1319	1.05 (0.97; 1.14)	1.07 (0.98; 1.17)
<i>P</i> for trend		NS	NS		NS	0.103
Fermented milk						
Q0	356	0.97 (0.86; 1.10)	0.96 (0.85; 1.08)	253	0.95 (0.83; 1.09)	0.96 (0.84; 1.10)
Q1 (reference)	1093	1.00	1.00	1388	1.00	1.00
Q2	1125	0.99 (0.91; 1.08)	0.99 (0.91; 1.08)	1065	0.93 (0.86; 1.01)	0.95 (0.87; 1.02)
Q3	1298	1.07 (0.99; 1.17)	1.07 (0.99; 1.16)	1308	0.93 (0.86; 1.01)	0.95 (0.88; 1.03)
Q4	1234	1.00 (0.92; 1.09)	1.01 (0.93; 1.11)	1150	0.93 (0.85; 1.00)	0.95 (0.87; 1.03)
Q5	1065	1.08 (0.99; 1.17)	1.08 (0.99; 1.17)	1217	0.92 (0.85; 1.00)	0.95 (0.87; 1.03)
<i>P</i> for trend		0.065	0.063		0.061	0.263
Butter						
Q0	526	0.92 (0.83; 1.02)	0.94 (0.85; 1.04)	758	0.95 (0.86; 1.04)	0.95 (0.86; 1.04)
Q1 (reference)	1205	1.00	1.00	1235	1.00	1.00
Q2	1122	0.98 (0.91; 1.07)	0.99 (0.91; 1.07)	1170	1.02 (0.95; 1.11)	1.03 (0.95; 1.11)
Q3	1151	1.01 (0.93; 1.09)	1.00 (0.92; 1.08)	1069	0.96 (0.88; 1.04)	0.96 (0.88; 1.04)
Q4	1124	0.98 (0.91; 1.07)	0.99 (0.91; 1.07)	1162	1.00 (0.92; 1.08)	1.00 (0.92; 1.08)
Q5	1043	0.95 (0.87; 1.03)	0.95 (0.87; 1.03)	1264	0.93 (0.85; 1.01)	0.95 (0.87; 1.03)
<i>P</i> for trend		NS	NS		NS	NS
Cheese						
Q0	173	0.98 (0.84; 1.15)	0.97 (0.83; 1.15)	142	0.89 (0.75; 1.06)	0.92 (0.77; 1.09)
Q1 (reference)	1110	1.00	1.00	1374	1.00	1.00
Q2	1213	1.03 (0.95; 1.12)	1.03 (0.95; 1.12)	1139	1.01 (0.94; 1.10)	1.02 (0.94; 1.10)
Q3	1046	1.05 (0.96; 1.14)	1.04 (0.96; 1.13)	1346	0.95 (0.88; 1.02)	0.95 (0.88; 1.03)
Q4	1428	1.07 (0.99; 1.15)	1.04 (0.96; 1.13)	1116	0.91 (0.85; 0.99)	0.92 (0.85; 1.00)
Q5	1201	1.00 (0.92; 1.09)	0.98 (0.90; 1.07)	1264	0.93 (0.86; 1.01)	0.95 (0.88; 1.04)
<i>P</i> for trend		NS	NS		0.008	0.039

Q0 = nonconsumers; Q1–Q5 are quintiles based on reported intake/day of each targeted dairy food item, ranked in sex, and 10-year age strata. *P* for trend >0.10 are summarized as nonsignificant (NS).

^aAdjusted for age, screening year, and dairy product category.

^bAdjusted for age, screening year, dairy product category, BMI, civil status, education level, physical activity in leisure time, smoking status, recruitment cohort (VIP or MONICA), and quintiles of fruit-and vegetables, alcohol, and energy intake.

and 6, subdivided into overall (Table 2), obesity-related (Table 3), smoking-related (Table 4), prostate and breast (Table 5), and colorectal cancer (Table 6).

In men, associations for most types of cancer were null. We observed a suggestive increased prostate cancer risk for cheese consumption in the adjusted model (HR Q5–Q1, 1.11; 95% CI, 0.97–1.27; *P* for trend = 0.013). Consumption of fermented milk was also associated with increased prostate cancer risk when comparing subjects in the lowest quintile with subjects in the highest in the basic model (HR Q5–Q1, 1.16; 95% CI, 1.02–1.32), but the result was attenuated in the fully adjusted model.

In women, hazards ratios for cheese consumption tended to be below one, with statistically significant trend tests for all cancer (HR Q5–Q1, 0.95; 95% CI, 0.88–1.04; *P* for trend = 0.039), smoking-related cancers (HR Q5–Q1, 0.84; 95% CI, 0.72–0.97; *P* for trend

≤ 0.001), and colorectal cancer (HR Q5–Q1, 0.82; 95% CI, 0.63–1.07; *P* for trend = 0.048).

Consumption of butter yielded a weak decreased obesity-related cancers risk in women (HR Q5–Q1, 0.91; 95% CI, 0.81–1.02; *P* for trend = 0.049). A decreased risk was also observed in the third vs. lowest quintile for smoking-related cancers.

Consumption of fermented milk showed a general pattern of HRs below one in women. No statistically significant linear trends were observed, but compared to the lowest quintile, decreased risks were observed for subjects in the highest quintile for obesity-related cancers, and the second and fourth quintile for breast cancer.

We found no linear relationships between consumption of non-fermented milk in women and any cancer endpoint. An increased risk was observed for women in the third vs. lowest quintile for all cancer, obesity-related cancers, and breast cancer.

Table 3. Hazard ratios (95% CIs) for intakes of dairy products and obesity-related cancer calculated from ^abasic and ^badjusted Cox proportional hazard models.

Obesity-related cancer	Men			Women		
	Cases	Basic ^a HR (95% CI)	Adjusted ^b HR (95% CI)	Cases	Basic ^a HR (95% CI)	Adjusted ^b HR (95% CI)
Non-fermented milk						
Q0	53	1.11 (0.82; 1.50)	1.10 (0.81; 1.49)	177	1.10 (0.93; 1.30)	1.10 (0.93; 1.30)
Q1 (reference)	209	1.00	1.00	586	1.00	1.00
Q2	174	0.93 (0.76; 1.14)	0.94 (0.77; 1.15)	533	1.02 (0.91; 1.14)	1.02 (0.91; 1.15)
Q3	230	0.98 (0.82; 1.19)	0.96 (0.80; 1.16)	832	1.12 (1.01; 1.25)	1.14 (1.02; 1.26)
Q4	244	1.07 (0.89; 1.28)	1.07 (0.89; 1.30)	556	1.03 (0.91; 1.15)	1.06 (0.94; 1.19)
Q5	185	0.91 (0.74; 1.10)	0.91 (0.74; 1.12)	716	1.07 (0.96; 1.20)	1.10 (0.98; 1.23)
<i>P</i> for trend		NS	NS		NS	NS
Fermented milk						
Q0	78	1.08 (0.83; 1.40)	1.06 (0.81; 1.37)	144	0.97 (0.81; 1.17)	0.98 (0.82; 1.18)
Q1 (reference)	213	1.00	1.00	760	1.00	1.00
Q2	196	0.89 (0.73; 1.08)	0.89 (0.73; 1.08)	551	0.88 (0.79; 0.98)	0.89 (0.80; 1.00)
Q3	226	0.97 (0.81; 1.18)	1.00 (0.82; 1.21)	690	0.90 (0.81; 1.00)	0.91 (0.82; 1.01)
Q4	199	0.89 (0.72; 1.09)	0.92 (0.75; 1.14)	615	0.89 (0.80; 1.00)	0.91 (0.82; 1.02)
Q5	183	0.92 (0.76; 1.11)	0.96 (0.78; 1.16)	640	0.87 (0.78; 0.97)	0.89 (0.79; 0.99)
<i>P</i> for trend		NS	NS		0.026	0.081
Butter						
Q0	94	0.92 (0.72; 1.17)	0.91 (0.71; 1.16)	415	0.93 (0.83; 1.05)	0.93 (0.82; 1.05)
Q1 (reference)	217	1.00	1.00	680	1.00	1.00
Q2	199	0.99 (0.81; 1.20)	0.99 (0.81; 1.20)	627	1.00 (0.89; 1.11)	1.00 (0.90; 1.12)
Q3	210	1.04 (0.86; 1.25)	1.02 (0.84; 1.23)	565	0.91 (0.81; 1.02)	0.92 (0.82; 1.03)
Q4	188	0.92 (0.76; 1.12)	0.93 (0.76; 1.13)	592	0.93 (0.83; 1.03)	0.94 (0.84; 1.05)
Q5	187	0.94 (0.77; 1.14)	0.93 (0.75; 1.14)	521	0.88 (0.79; 0.99)	0.91 (0.81; 1.02)
<i>P</i> for trend		NS	NS		0.011	0.049
Cheese						
Q0	27	0.81 (0.54; 1.21)	0.84 (0.56; 1.26)	68	0.80 (0.63; 1.03)	0.86 (0.67; 1.10)
Q1 (reference)	211	1.00	1.00	723	1.00	1.00
Q2	217	0.99 (0.82; 1.19)	1.00 (0.83; 1.21)	628	1.06 (0.96; 1.18)	0.84 (0.65; 1.07)
Q3	204	1.09 (0.90; 1.33)	1.11 (0.92; 1.36)	696	0.93 (0.84; 1.03)	0.94 (0.84; 1.04)
Q4	219	0.86 (0.71; 1.04)	0.88 (0.72; 1.07)	614	0.96 (0.87; 1.07)	0.96 (0.86; 1.07)
Q5	217	0.95 (0.79; 1.15)	0.96 (0.78; 1.17)	671	0.94 (0.85; 1.05)	0.97 (0.86; 1.09)
<i>P</i> for trend		NS	NS		NS	NS

Q0 = nonconsumers; Q1–Q5 are quintiles based on reported intake/day of each targeted dairy food item, ranked in sex, and 10-year age strata. *P* for trend >0.10 are summarized as nonsignificant (NS).

^aAdjusted for age, screening year, and dairy product category.

^bAdjusted for age, screening year, dairy product category, BMI, civil status, education level, physical activity in leisure time, smoking status, recruitment cohort (VIP or MONICA), and quintiles of fruit-and vegetables, alcohol, and energy intake.

Our sensitivity analyses did not render any heterogeneous results.

Discussion

The results of this large, prospective, population-based cohort study, from a population with a high consumption of dairy products, does not support any major impact on cancer risk from consumption of four main categories of dairy products. In men, null results were observed except an increased risk of prostate cancer by increased intake of cheese. In women, a high cheese consumption was associated with a modest decreased risk of all cancer, smoking-related and colorectal cancers, and hazards ratios for fermented milk were generally below one though not statistically significant. These findings are consistent with other cohort studies around the world (9–11,16–30,45,46), with the WCRF's continuous update project (4), and

to some extent also with another study performed in the same study population, where high intakes of fermented milk and cheese were associated with a lower mortality (47).

The positive association between cheese consumption and prostate cancer risk may be attributed to the very high calcium content of cheese in comparison with other dairy products. This would be consistent with calcium being widely demonstrated as likely to increase the risk of prostate cancer (11). The decreased risk of all cancer, and smoking-related and colorectal cancers in particular, with increased intake of cheese in women could similarly be attributed to causal pathways including lactoferrin (12), dairy lipids (15), and positive effects on the gut microbiome (4). Still it cannot be excluded that these associations are reflections of nondairy associated food items.

The decreased risk of obesity-related cancers with increased intake of butter in woman is difficult to

Table 4. Hazard ratios (95% CIs) for intakes of dairy products and smoking-related cancer calculated from ^abasic and ^badjusted Cox proportional hazard models.

Smoking-related cancer	Men			Women		
	Cases	Basic ^a HR (95% CI)	Adjusted ^b HR (95% CI)	Cases	Basic ^a HR (95% CI)	Adjusted ^b HR (95% CI)
Non-fermented milk						
Q0	93	1.14 (0.9; 1.43)	1.11 (0.89; 1.40)	119	1.12 (0.91; 1.38)	1.09 (0.89; 1.35)
Q1 (reference)	358	1.00	1.00	378	1.00	1.00
Q2	310	0.97 (0.83; 1.13)	0.98 (0.84; 1.14)	305	0.89 (0.76; 1.03)	0.90 (0.77; 1.05)
Q3	421	1.04 (0.90; 1.20)	1.02 (0.89; 1.18)	495	1.04 (0.91; 1.19)	1.05 (0.92; 1.21)
Q4	402	1.02 (0.88; 1.17)	1.01 (0.87; 1.17)	333	0.94 (0.81; 1.09)	0.98 (0.84; 1.14)
Q5	356	1.00 (0.87; 1.16)	0.99 (0.85; 1.16)	415	0.96 (0.83; 1.10)	0.94 (0.81; 1.09)
P for trend		NS	NS		NS	NS
Fermented milk						
Q0	136	1.07 (0.88; 1.31)	1.06 (0.87; 1.29)	84	0.95 (0.75; 1.20)	0.98 (0.78; 1.24)
Q1 (reference)	376	1.00	1.00	474	1.00	1.00
Q2	357	0.92 (0.79; 1.06)	0.95 (0.82; 1.10)	338	0.93 (0.81; 1.06)	0.97 (0.84; 1.11)
Q3	409	0.98 (0.86; 1.13)	1.06 (0.92; 1.22)	402	0.85 (0.74; 0.98)	0.91 (0.79; 1.05)
Q4	349	0.89 (0.76; 1.04)	0.99 (0.85; 1.16)	345	0.83 (0.72; 0.96)	0.92 (0.80; 1.07)
Q5	313	0.90 (0.78; 1.04)	1.01 (0.87; 1.18)	402	0.91 (0.79; 1.04)	1.01 (0.87; 1.16)
P for trend		NS	NS		NS	NS
Butter						
Q0	170	0.97 (0.81; 1.17)	0.96 (0.8; 1.15)	235	0.97 (0.82; 1.14)	0.97 (0.82; 1.14)
Q1 (reference)	368	1.00	1.00	373	1.00	1.00
Q2	341	1.00 (0.86; 1.16)	1.01 (0.87; 1.17)	353	1.03 (0.89; 1.19)	1.04 (0.90; 1.20)
Q3	366	1.07 (0.92; 1.24)	1.02 (0.88; 1.18)	361	1.08 (0.94; 1.25)	1.07 (0.92; 1.23)
Q4	360	1.03 (0.89; 1.19)	1.00 (0.86; 1.16)	426	1.20 (1.04; 1.38)	1.17 (1.01; 1.34)
Q5	335	0.99 (0.86; 1.15)	0.94 (0.80; 1.10)	297	0.93 (0.80; 1.08)	0.94 (0.80; 1.10)
P for trend		NS	NS		NS	NS
Cheese						
Q0	56	0.93 (0.70; 1.23)	0.90 (0.67; 1.20)	43	0.75 (0.55; 1.02)	0.76 (0.56; 1.04)
Q1 (reference)	382	1.00	1.00	488	1.00	1.00
Q2	376	0.94 (0.81; 1.08)	0.94 (0.81; 1.08)	348	0.87 (0.76; 1.00)	0.90 (0.78; 1.03)
Q3	343	1.01 (0.88; 1.17)	1.03 (0.89; 1.20)	451	0.87 (0.77; 0.99)	0.90 (0.79; 1.03)
Q4	407	0.88 (0.77; 1.02)	0.89 (0.77; 1.03)	324	0.74 (0.64; 0.84)	0.78 (0.67; 0.89)
Q5	376	0.89 (0.77; 1.03)	0.91 (0.78; 1.05)	391	0.78 (0.68; 0.89)	0.84 (0.72; 0.97)
P for trend		NS	NS		<0.001	<0.001

Q0 = nonconsumers; Q1–Q5 are quintiles based on reported intake/day of each targeted dairy food item, ranked in sex, and 10-year age strata. P for trend >0.10 are summarized as nonsignificant (NS).

^aAdjusted for age, screening year, and dairy product category.

^bAdjusted for age, screening year, dairy product category, BMI, civil status, education level, physical activity in leisure time, smoking status, recruitment cohort (VIP or MONICA), and quintiles of fruit-and vegetables, alcohol, and energy intake.

interpret. A possible explanation could be under-reporting of butter consumption by obese women. However, the association is weak, and thus it cannot be excluded that it is a random finding.

Results were inconsistent between the sexes, with stronger associations found in women and HRs in many cases suggesting diametrically different risk-associations by sex. In other studies, the opposite has been shown, for example, a stronger protective effect from dairy products on colorectal cancers in men (48). However, potential sex differences should be interpreted with caution given the relatively small effect sizes and generally nonstatistically significant results in the present study.

The main limitation of this study was the use of an FFQ to estimate dietary intake. Only predefined food items are recorded, and the methodology is biased by both under- and over-reporting. However, according to a 24-h-recall validation of the NSDD

FFQ, the accuracy of reported dairy product intake is satisfactory (39). Another limitation was the use of dietary intake data collected at a single time point. Dietary patterns have changed in the study cohort over the past decades, with increasing adherence to authority guideline during the period 1985–2005 and toward a higher-fat, lower-carbohydrate diet since then (49), which might have biased our results toward the null. We used the same sets of covariates in the basic and fully adjusted models, respectively, for all cancer endpoints. In the fully adjusted models, no changes in the direction and minimal changes in the risk magnitudes appeared compared to the basic models, indicating a minimal risk of over-adjustment, and suggesting that the associations observed are likely to reflect consumption of dairy products to a large extent. However, we cannot exclude the possibility of residual confounding due to other, or insufficiently captured,

Table 5. Hazard ratios (95% CIs) for intakes of dairy products and prostate cancer in men and breast cancer in women calculated from ^abasic and ^badjusted Cox proportional hazard models.

	Prostate cancer in men			Breast cancer in women		
	Cases	Basic ^a HR (95% CI)	Adjusted ^b HR (95% CI)	Cases	Basic ^a HR (95% CI)	Adjusted ^b HR (95% CI)
Non-fermented milk						
Q0	109	1.02 (0.83; 1.25)	1.02 (0.83; 1.26)	100	1.13 (0.90; 1.42)	1.14 (0.91; 1.43)
Q1 (reference)	474	1.00	1.00	315	1.00	1.00
Q2	428	1.00 (0.88; 1.14)	1.01 (0.89; 1.15)	332	1.17 (1.00; 1.36)	1.16 (0.99; 1.36)
Q3	570	1.08 (0.95; 1.22)	1.04 (0.92; 1.17)	461	1.18 (1.03; 1.37)	1.19 (1.03; 1.37)
Q4	504	0.98 (0.86; 1.11)	0.96 (0.85; 1.10)	313	1.07 (0.91; 1.25)	1.09 (0.93; 1.28)
Q5	457	0.99 (0.87; 1.12)	1.00 (0.87; 1.15)	400	1.13 (0.98; 1.31)	1.17 (1.00; 1.36)
P for trend		NS	NS		NS	NS
Fermented milk						
Q0	142	0.97 (0.80; 1.18)	0.95 (0.78; 1.15)	76	0.91 (0.71; 1.17)	0.92 (0.72; 1.18)
Q1 (reference)	424	1.00	1.00	417	1.00	1.00
Q2	483	1.07 (0.94; 1.21)	1.04 (0.91; 1.19)	310	0.84 (0.73; 0.98)	0.85 (0.73; 0.98)
Q3	522	1.11 (0.98; 1.26)	1.06 (0.93; 1.21)	398	0.93 (0.81; 1.07)	0.92 (0.80; 1.06)
Q4	547	1.08 (0.94; 1.24)	1.05 (0.91; 1.20)	339	0.88 (0.76; 1.02)	0.86 (0.74; 1.00)
Q5	424	1.16 (1.02; 1.32)	1.09 (0.95; 1.24)	381	0.9 (0.78; 1.04)	0.88 (0.76; 1.02)
P for trend		NS	NS		NS	NS
Butter						
Q0	198	0.84 (0.71; 0.99)	0.86 (0.72; 1.01)	243	0.97 (0.82; 1.14)	0.97 (0.82; 1.14)
Q1 (reference)	492	1.00	1.00	381	1.00	1.00
Q2	475	1.02 (0.90; 1.16)	1.02 (0.89; 1.15)	342	0.96 (0.83; 1.11)	0.95 (0.82; 1.10)
Q3	479	1.01 (0.89; 1.15)	1.00 (0.88; 1.13)	318	0.90 (0.77; 1.04)	0.90 (0.77; 1.04)
Q4	455	0.99 (0.87; 1.12)	0.99 (0.87; 1.13)	323	0.89 (0.77; 1.03)	0.90 (0.78; 1.05)
Q5	443	0.98 (0.86; 1.11)	0.97 (0.85; 1.11)	314	0.93 (0.80; 1.08)	0.94 (0.81; 1.10)
P for trend		NS	NS		NS	NS
Cheese						
Q0	73	1.07 (0.84; 1.37)	1.08 (0.84; 1.39)	41	0.88 (0.64; 1.21)	0.92 (0.66; 1.26)
Q1 (reference)	426	1.00	1.00	398	1.00	1.00
Q2	494	1.13 (0.99; 1.28)	1.12 (0.99; 1.28)	353	1.09 (0.94; 1.26)	1.07 (0.93; 1.24)
Q3	418	1.12 (0.98; 1.28)	1.11 (0.97; 1.28)	384	0.95 (0.82; 1.09)	0.93 (0.80; 1.07)
Q4	617	1.23 (1.09; 1.40)	1.19 (1.05; 1.35)	350	1.02 (0.88; 1.17)	0.97 (0.84; 1.12)
Q5	514	1.14 (1.00; 1.30)	1.11 (0.97; 1.27)	395	1.02 (0.89; 1.18)	0.99 (0.85; 1.16)
P for trend		0.001	0.013		NS	NS

Q0 = nonconsumers; Q1–Q5 are quintiles based on reported intake/day of each targeted dairy food item, ranked in sex, and 10-year age strata. P for trend >0.10 are summarized as nonsignificant (NS).

^aAdjusted for age, screening year, and dairy product category.

^bAdjusted for age, screening year, dairy product category, BMI, civil status, education level, physical activity in leisure time, smoking status, recruitment cohort (VIP or MONICA), and quintiles of fruit-and vegetables, alcohol, and energy intake.

life style factors associated with dairy consumption and cancer.

The strengths of this study included the detailed information about dairy product intakes, including 10 different food items within the four dairy product groups, that is, non-fermented milk, fermented milk, butter, and cheese, the wide distribution of dairy intakes, the prospectively collected data, the long follow-up time, and the culturally and genetically fairly homogenous population of arctic Sweden. The large cohort size allowed us to exclude nonconsumers from the trend analyses, which improves the reliability of the results, as we have previously shown (50). In brief, when defining low consumers as the reference category, subjects abstaining from dairy products were shown to be at greater risk of having a disadvantageous cardiometabolic risk

profile than high consumers. Furthermore, the population-based nature of the cohort (36) ensures generalizability of the results.

Conclusion

Based on the findings of this large, prospective population-based cohort study, we cannot predict any major adverse or beneficial effects of consuming dairy products from a cancer prevention perspective. Any potential beneficial effect of dairy products on cancer health is most likely associated with cheese and fermented milk rather than non-fermented milk or butter. Future studies should aim for identifying dairy product-specific biomarker for use in large studies encompassing populations with

Table 6. Hazard ratios (95% CIs) for intakes of dairy products and colorectal cancer calculated from ^abasic and ^badjusted Cox proportional hazard models.

Colorectal cancer	Men			Women		
	Cases	Basic ^a HR (95% CI)	Adjusted ^b HR (95% CI)	Cases	Basic ^a HR (95% CI)	Adjusted ^b HR (95% CI)
Non-fermented milk						
Q0	38	1.23 (0.86; 1.76)	1.23 (0.86; 1.76)	35	0.99 (0.68; 1.44)	1.00 (0.69; 1.45)
Q1 (reference)	135	1.00	1.00	132	1.00	1.00
Q2	104	0.86 (0.67; 1.12)	0.87 (0.67; 1.12)	96	0.82 (0.63; 1.07)	0.84 (0.64; 1.09)
Q3	159	1.05 (0.83; 1.32)	1.01 (0.80; 1.28)	170	0.98 (0.78; 1.23)	1.02 (0.81; 1.28)
Q4	162	1.08 (0.86; 1.36)	1.10 (0.87; 1.39)	109	0.89 (0.69; 1.14)	0.97 (0.75; 1.26)
Q5	115	0.86 (0.67; 1.11)	0.87 (0.67; 1.14)	126	0.81 (0.63; 1.03)	0.88 (0.68; 1.14)
<i>P</i> for trend		NS	NS		NS	NS
Fermented milk						
Q0	56	1.20 (0.88; 1.63)	1.18 (0.86; 1.62)	35	1.15 (0.79; 1.66)	1.16 (0.80; 1.69)
Q1 (reference)	138	1.00	1.00	166	1.00	1.00
Q2	126	0.88 (0.69; 1.12)	0.88 (0.69; 1.12)	99	0.86 (0.68; 1.10)	0.89 (0.70; 1.13)
Q3	140	0.93 (0.73; 1.17)	0.94 (0.74; 1.19)	127	0.78 (0.61; 0.99)	0.80 (0.61; 1.02)
Q4	132	0.87 (0.68; 1.13)	0.91 (0.70; 1.18)	112	0.78 (0.61; 1.00)	0.82 (0.63; 1.05)
Q5	121	0.96 (0.76; 1.21)	0.98 (0.77; 1.25)	129	0.84 (0.66; 1.06)	0.90 (0.70; 1.15)
<i>P</i> for trend		NS	NS		NS	NS
Butter						
Q0	61	0.98 (0.72; 1.33)	0.97 (0.71; 1.33)	83	0.95 (0.72; 1.25)	0.94 (0.71; 1.24)
Q1 (reference)	132	1.00	1.00	133	1.00	1.00
Q2	136	1.12 (0.88; 1.43)	1.13 (0.89; 1.44)	128	1.05 (0.83; 1.34)	1.06 (0.83; 1.36)
Q3	142	1.16 (0.91; 1.47)	1.13 (0.89; 1.44)	112	0.95 (0.74; 1.23)	0.95 (0.74; 1.22)
Q4	121	0.97 (0.76; 1.24)	0.97 (0.75; 1.25)	125	1.00 (0.78; 1.28)	1.04 (0.81; 1.34)
Q5	121	1.00 (0.78; 1.29)	0.99 (0.76; 1.28)	87	0.76 (0.58; 1.00)	0.82 (0.62; 1.08)
<i>P</i> for trend		NS	NS		NS	NS
Cheese						
Q0	18	0.78 (0.48; 1.28)	0.82 (0.50; 1.34)	16	0.88 (0.52; 1.47)	0.92 (0.55; 1.54)
Q1 (reference)	146	1.00	1.00	149	1.00	1.00
Q2	134	0.88 (0.69; 1.11)	0.89 (0.70; 1.13)	123	1.00 (0.79; 1.27)	1.01 (0.80; 1.29)
Q3	135	1.05 (0.83; 1.32)	1.07 (0.85; 1.36)	149	0.92 (0.73; 1.15)	0.95 (0.75; 1.19)
Q4	142	0.80 (0.64; 1.02)	0.81 (0.64; 1.03)	109	0.83 (0.66; 1.06)	0.84 (0.66; 1.08)
Q5	138	0.86 (0.68; 1.09)	0.86 (0.67; 1.10)	122	0.76 (0.59; 0.97)	0.82 (0.63; 1.07)
<i>P</i> for trend		NS	NS		0.010	0.048

Q0 = nonconsumers; Q1–Q5 are quintiles based on reported intake/day of each targeted dairy food item, ranked in sex, and 10-year age strata. *P* for trend >0.10 are summarized as nonsignificant (NS).

^aAdjusted for age, screening year, and dairy product category.

^bAdjusted for age, screening year, dairy product category, BMI, civil status, education level, physical activity in leisure time, smoking status, recruitment cohort (VIP or MONICA), and quintiles of fruit-and vegetables, alcohol, and energy intake.

a wide range, including high intakes of specific dairy product categories.

Author contributions

IJ, AW, and LMN conceptualized the study; IJ performed the formal analyses; LMN, IJ, and AW prepared the original draft; BVG, AE, J-H J, and PW contributed medical and epidemiological expertise, reviewed, and contributed to the final version of the manuscript. All authors read and approved the final version. IJ, AW, and LMN acquired the funding.

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