REVIEW

Dairy Consumption and Total Cancer and Cancer-Specific Mortality: A Meta-Analysis of Prospective Cohort Studies

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ABSTRACT

The association between dairy consumption and cancer mortality varies among studies and remains unclear. Thus, we conducted a comprehensive meta-analysis of prospective cohort studies to examine the association between dairy consumption and total cancer and cancer-specific mortality. We sought eligible studies in PubMed and Web of Science databases for all publications through March 2021, and pooled RRs and 95% CIs were calculated. We identified 34 prospective cohort studies including 3,171,186 participants and 88,545 deaths. Compared with low milk consumption, high milk consumption was associated with higher cancer mortality in females (RR: 1.10; 95% CI: 1.01, 1.21) and people consuming high/whole-fat milk (fat content ≥3.5%) (RR: 1.17; 95% CI: 1.07, 1.28). Increased risks of cancer-specific mortality were detected for liver (RR: 1.13; 95% CI: 1.02, 1.26), ovarian (RR: 1.32; 95% CI: 1.13, 1.55), and prostate (RR: 1.23; 95% CI: 1.02, 1.48) cancers. Also, females with high consumption of fermented milk had a lower cancer mortality risk (RR: 0.85; 95% CI: 0.77, 0.94). High cheese consumption was not associated with total cancer mortality but rather with higher colorectal cancer mortality (RR: 1.22; 95% CI: 1.02, 1.46). There was no association between butter (RR: 1.06; 95% CI: 0.70, 1.59) or total dairy product consumption (RR: 0.99; 95% CI: 0.95, 1.03) and cancer mortality. Our results imply that high milk consumption, especially high/whole-fat milk, was associated with higher cancer mortality, whereas fermented milk consumption was associated with lower cancer mortality, and this was particularly evident in females. Consequently, further studies are warranted. *Adv Nutr* 2022;13:1063–1082.

Statement of Significance: This meta-analysis indicated that high-fat milk consumption might be associated with higher cancer mortality, whereas fermented milk consumption is inversely associated with cancer mortality.

Keywords: dairy products, milk, fermented milk, cancer, mortality, meta-analysis

Introduction

Cancer is a leading cause of death globally. The WHO reported that cancer accounted for nearly 10 million deaths in 2020 (1). Dairy products are recommended in most dietary guidelines worldwide. Dairy products are a complex blend of bioactive compounds that have both positive and negative impacts on carcinogenesis (2). However, the contents of dairy products differ based on the type of dairy product; therefore, each dairy product may not have the same effect on cancer. The World Cancer Research Foundation International (WCRF) reported that the consumption of dairy products probably protects against colorectal cancer (3). In addition, the WCRF also reported that the consumption of dairy products may reduce the risk of breast cancer and increase the risk of prostate cancer, but the evidence is limited (3). These results imply that dairy products consumption may have varying effects depending on the cancer site.

A few prospective cohort studies have examined the association between dairy products consumption and cancer mortality in the general population, but the association remains inconsistent. Previously, 3 meta-analyses on dairy consumption and cancer mortality showed no significant association between dairy consumption and cancer mortality (4–6). In the analyses, the results of mortality from specific cancers were included for total cancer mortality, such as

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Abbreviations used: IGF-1, insulin-like growth factor 1; WCRF, World Cancer Research Foundation International.

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prostate cancer mortality. One meta-analysis that included studies conducted in the United States only examined total dairy consumption without analyzing other types of dairy products (5). Another meta-analysis assessed total consumption of dairy products and milk without analyzing fermented milk, cheese, or other types of dairy products (6). Although Lu et al. (4) conducted a meta-analysis of several types of dairy products and cancer mortality risk, the subgroup analysis had many limitations due to few studies included in the analysis. In addition, no comprehensive meta-analysis of dairy products consumption on cancer-specific mortality risk has been conducted to date.

Therefore, we conducted a comprehensive meta-analysis to quantitatively assess the association between the consumption of total dairy products and subtypes of dairy products, including milk, fermented milk (which includes yogurt and soured milk), cheese, and butter, and total cancer mortality. Furthermore, we conducted subgroup analyses stratified by sex, cancer site, fat content, geographic region, and adjustment factors.

Methods

Literature search and study selection

We conducted a literature search for all publications through March 2021 as full-length articles and written in English using PubMed and ISI Web of Science. The search terms were as follows: "(dairy OR milk OR cheese OR yogurt OR yoghurt OR butter)" AND "(neoplasia OR neoplasm OR cancer OR carcinoma OR tumor OR tumour)" AND "(mortality OR death OR fatal OR survival)." This meta-analysis included studies that satisfied the following criteria: *1*) the study was designed prospectively; *2*) the exposure was dairy product consumption, including total dairy, milk, fermented milk, cheese, and butter; *3*) the outcomes were all cancer mortality or cancer-specific mortality; and *4*) the study reported RRs and CIs. We excluded studies that examined mortality risk in participants with the disease at baseline. Also, if more than 1 publication from the same cohort was available, we selected the publication with a long follow-up period or a high number of cases.

Data extraction

Both authors (SJ and YJ) independently extracted data according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (7). Each study provided the following information: the first author's last name, year of publication, geographical region and cohort name, follow-up period, baseline age, the number of participants, the number of deaths, each category of dairy products consumption, RR and 95% CI for the association between each dairy product consumption category and cancer mortality, and adjustment factors. We adopted the RR that reflected the most adjustment degree for potential confounding factors if the study provided multiple RRs for this association.

Quality assessment

The Newcastle–Ottawa Scale was used to evaluate the quality of studies included in the meta-analysis (8). We examined the quality of each study in the following aspects: the selection of study participants, comparability, and outcome assessment. Studies with scores of 10 or higher (out of 13) were considered high quality, 7–9 as good quality, and 6 or lower as low quality.

Statistical analysis

The DerSimonian and Laird random-effects models (9), which incorporated both within- and between-studies variations, were used to estimate pooled RR of cancer mortality for the highest compared with lowest consumption of total dairy, milk, fermented milk (which includes yogurt and soured milk), cheese, and butter. When a study reported results of specific cancer and other cancers but not total cancer, we used a fixed-effect model to get an overall estimate of total cancer before combining it with other studies (10). If the study reported individual RRs for whole milk, low-fat milk, and skim milk but not total milk, we used a fixed-effect model to get an overall estimate of total milk or low/skimmed milk before merging it with additional studies (11–15). We conducted subgroup analyses stratified by sex, cancer site, fat content (high/whole fat or low/nonfat), and geographic region (United States, Asia, Europe, or Oceania). We classified cancer sites as upper digestive tract (mouth cancer, pharynx cancer, and esophageal cancer), gastrointestinal tract (stomach cancer, colorectal cancer, and anal cancer), hepatobiliary system (liver cancer, gallbladder cancer, pancreatic cancer, and bile duct cancer), respiratory tract (lung cancer, nasopharyngeal cancer, and larynx cancer), women's cancer (breast cancer, cervical cancer, endometrial cancer, and ovarian cancer), men's cancer (prostate cancer), and urological system (kidney cancer and bladder cancer). Furthermore, we examined whether the studies had accounted for crucial confounders such as BMI, total energy intake, alcohol consumption, smoking status, physical activity, and socioeconomic status, conducting stratified analysis by the adjustment factors. The Q statistic assessed heterogeneity among studies included in the meta-analysis (16), and the I^2 statistic quantified inconsistency (17). Sensitivity analyses were conducted by excluding each study one at a time.

Dose-response analyses were conducted using the method by Greenland and Longnecker (18–20) to calculate the study-specific slopes across dairy products intake categories. The analysis was conducted for studies that provided RRs with at least 3 exposure categories and the distribution of deaths and person years or subjects in each dairy products intake category. We calculated the midpoint value for each dairy products intake category if a study presented the intake as a range. We adopted the interval of the adjacent category if the highest category was open-ended. If a study reported consumption as a serving, we converted the unit to 177 g for total dairy, 244 g for milk or fermented milk, and 43 g for cheese, as provided in the USDA Food and Nutrient

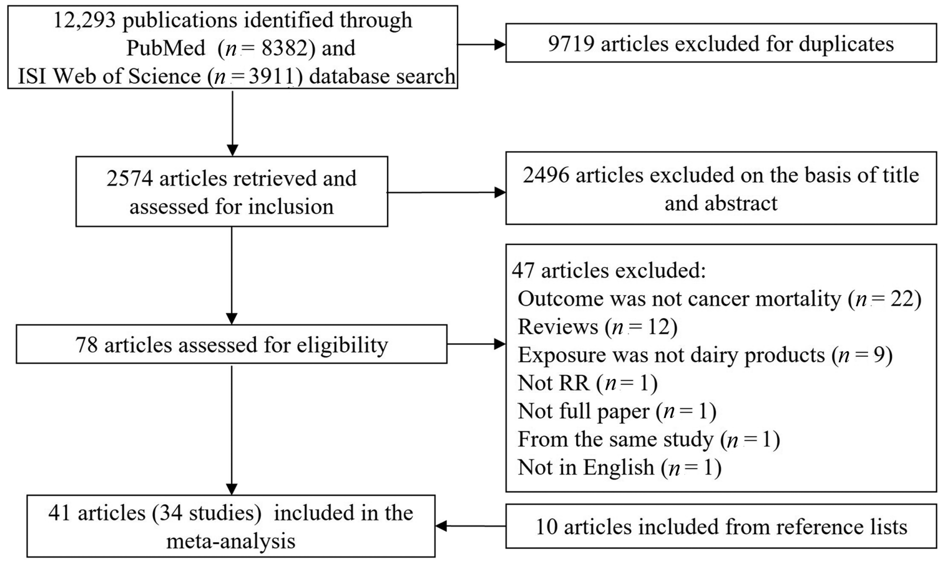

FIGURE 1 Flow diagram of the study selection.

Database for Dietary Studies (21). Begg (22) and Egger (23) tests were used for examining potential publication bias. A 2-tailed $P < 0.05$ was considered statistically significant. Stata/SE version 14.2 was used for statistical analyses (StataCorp).

Results

Study characteristics

A total of 34 studies (41 publications from 1984 to 2021) (5, 10–15, 24–57) with 3,171,186 participants and 88,545 deaths were included (**Figure 1**). **Table 1** shows the characteristics of prospective cohort studies included in the meta-analysis. Seventeen studies were conducted in the United States (5, 11–15, 24–26, 28–31, 34, 38, 41, 43, 51, 53, 54, 57), 8 studies in Asia (27, 32, 33, 35–37, 39, 40, 44, 47, 48, 56), 8 studies in Europe (10, 45, 46, 49, 50, 52, 55), and 1 study in Oceania (42). Cohort studies included a follow-up period ranging from 4.2 to 41 y with a median follow-up time of 14.15 y, and participants were aged ≥15 y at baseline. All studies adjusted for age, and most studies adjusted for BMI ($n = 25$) (5, 10, 12–15, 34, 36, 38, 40–49, 51–56), total energy intake ($n = 21$) (5, 12–15, 31, 38, 41–43, 45, 46, 48, 50–54, 56, 57), alcohol consumption ($n = 24$) (5, 10, 12–15, 31, 36, 38, 42, 43, 45–57), smoking status ($n = 30$) (5, 10–15, 28–38, 41–43, 45–57), physical activity ($n = 23$) (5, 12–15, 36, 38, 40–43, 45–57), and socioeconomic status ($n = 22$) (5, 10, 12, 14, 26, 30, 34, 36, 40–49, 52, 55–57). In terms of quality assessment, the studies included in the meta-analysis had a mean score of 11.1 out of 13, except for 1 study having a score of 8, which indicates good quality (27), and all studies had a score of >9, indicating high quality.

Total dairy consumption and cancer mortality

Thirteen prospective cohort studies including 1,112,975 participants and 43,096 deaths investigated the association between total dairy consumption and total cancer mortality. The pooled RR for highest compared with lowest consumption was 0.99 (95% CI: 0.95, 1.03) with no significant heterogeneity among the studies ($I^2 = 24.9\%$, $P = 0.20$) (**Table 2**, **Figure 2**). No significant associations were detected when stratified by sex, cancer site, fat content, or adjustment for covariates, and meta-regression analysis revealed no significant differences (P-difference ≥ 0.1 for all comparisons). By the geographic region, pooled RRs were 1.02 in the United States (95% CI: 0.98, 1.06), 0.82 in Asia (95% CI: 0.66, 1.02), 0.94 in Oceania (95% CI: 0.42, 2.11), and 0.91 in Europe (95% CI: 0.84, 0.98). Although the significant inverse association was discovered in Europe, only 1 study was included in the analysis (P-difference for Europe compared with the United States = 0.04). The dose-response analysis for total dairy consumption and total cancer mortality included 10 studies (5, 14, 15, 44, 48, 51, 56, 57) (**Table 3**). The pooled RR for the 400-g/d increment of total dairy consumption was 1.00 (95% CI: 0.97, 1.04). Although the pooled RR for an increase of 400 g/d in total dairy consumption was 1.07 (95% CI: 1.00, 1.14) in males, only 1 study was included in this dose-response analysis. There was no significant association detected when the analysis was stratified by fat content.

Milk consumption and cancer mortality

The association between milk consumption and total cancer mortality was evaluated in 17 prospective cohort studies, including 967,559 participants and 56,471 deaths. The pooled RR for highest compared with lowest consumption

TABLE 1 Characteristics of the prospective cohort studies included in the meta-analysis[1]

First author, year	Country	Cohort name	Follow-up period	Age at baseline, y	Participants	No. of deaths	Exposure category	Cancer type	Adjustment for covariates[2]	NOS score
Snowdon, 1984 (24)	United States	California Seventh-Day Adventists	21 y	≥30	6763	99	Milk <1 (ref), 1–2, ≥3 glasses/d Cheese <1 (ref), 1–2, ≥3 d/wk	Prostate	1	10
Phillips, 1985 (25)	United States	California Seventh-Day Adventists	21 y	≥30	25,493	182	Milk <1 (ref), 1–2, ≥3/d Cheese <1 (ref), 1–2, ≥3/wk	Colorectal	1, 2	10
Mills, 1988 (26)	United States	California Seventh-Day Adventists	21 y	30–85	994	142	Milk None/occasional (ref), 1, 2, ≥3 drinks/d Cheese None/occasional (ref), 1, 2, ≥3 d/wk	Breast	9, 13, 14, 15, 16, 17, 18, 19	10
Hirayama, 1990 (27)	Japan	Japan 6 Prefectures Cohort Study	17 y	≥40	265,118	14,740	Milk Nondaily (ref), daily	Mouth, pharynx, esophagus, stomach, colon, rectum, liver, gallbladder, pancreas, nasal sinus, larynx, lung, breast, cervix uteri, ovary, prostate, kidney, bladder	1, 2	8
Hsing, 1990 (28)	United States	The Lutheran Brotherhood Cohort	20 y	≥35	17,633	149	Dairy <26 (ref), 27–51, 52–85, 86–189 times/mo	Prostate	1, 5	12
Kneller, 1991 (29)	United States	The Lutheran Brotherhood Cohort	20 y	≥35	17,633	75	Dairy Q1 (ref), Q2, Q3, Q4 Milk <1 (ref), 1, 2–3, ≥4 glasses/d	Stomach	1, 5	12
Chow, 1992 (30)	United States	The Lutheran Brotherhood Cohort	20 y	≥35	17,633	219	Dairy <46 (ref), 46–95, 96–142, >142 times/mo	Lung	1, 5, 10	12
Hsing, 1998 (31)	United States	The Lutheran Brotherhood Cohort	20 y	≥35	17,633	145	Dairy <26.0 (ref), 26.0–50.0, 51.0–85.0, >85.0 times/mo	Colorectal	1, 5, 6, 7	12
Breslow, 2000 (11)	United States	The National Health Interview Survey	8.5 y	18–87	20,195	158	Dairy 0–3.0 (ref), 3.0–7.0, 7.0–10.0, >10.0 servings/wk Whole milk 0 (ref), 0.02–7, >8.0 servings/wk Low-fat milk 0 (ref), 0.02–7, >8.0 servings/wk Skim milk 0 (ref), 0.02–5, >5.6 servings/wk Cheese 0–0.5 (ref), 0.5–1.9, 2.0–3.0, >3.0 servings/wk	Lung	1, 2, 5	11

(*Continued*)

TABLE 1 (*Continued*)

First author, year	Country	Cohort name	Follow-up period	Age at baseline, y	Participants	No. of deaths	Exposure category	Cancer type	Adjustment for covariates[2]	NOS score
Ozasa, 2001 (32)	Japan	The Japan Collaborative Cohort	92 mo	40–79	98,248	572	Milk Scarcely any (ref), 1–2/mo to 3–4/wk, almost every day Yogurt Scarcely any (ref), 1–2/mo to 1–2/wk, ≥3–4/wk Cheese Scarcely any (ref), 1–2/mo to 1–2/wk, ≥3–4/wk Butter Scarcely any (ref), 1–2/mo to 1–2/wk, ≥3–4/wk	Lung	1, 5, 12	10
Ness, 2001 (10)	United Kingdom	The Collaborative study	25 y	35–64	5765	714	Milk None (ref), 1, >1 pint/d	Lung, other cancer	1, 4, 5, 7, 9, 11, 20, 21, 22, 23, 24	10
Rodriguez, 2002 (34)	United States	Cancer Prevention Studies I	13 y	52	417,018	1751	Dairy <7 (ref), 7–14, 15–28, ≥28 servings/wk	Prostate	1, 4, 5, 9, 12, 25	12
Rodriguez, 2002 (34)	United States	Cancer Prevention Studies II	14 y	57	447,780	3594	Dairy <7 (ref), 7–14, 15–28, ≥28 servings/wk	Prostate	1, 4, 5, 9, 12, 25	12
Ngoan, 2002 (33)	Japan		13 y	15–96	13,250	116	Dairy ≤2–4 times/mo (ref), 2–4 times/wk, ≥1/d Milk ≤2–4 times/mo (ref), 2–4 times/wk, ≥1/d	Stomach	1, 2, 5, 17, 26, 27, 28, 29	12
Kojima, 2004 (36)	Japan	The Japan Collaborative Cohort	9.9 y	40–79	107,824	457	Milk Seldom (ref), 0.5–4/wk, every day Yogurt Seldom (ref), 1–2/mo, 1–7/wk Cheese Seldom (ref), 1–2/mo, 1–7/wk Butter Seldom (ref), 1–2/mo, 1–7/wk	Colon, rectal	1, 4, 5, 7, 8, 9, 12, 30	10
Khan, 2004 (35)	Japan	Hokkaido Cohort Study	M: 13.8 y F: 14.8 y	40–97	3158	244	Milk Never + several times/y + several times/mo (ref), several times/wk + every day Yogurt Never + several times/y + several times/mo (ref), several times/wk + every day Cheese Never + several times/y + several times/mo (ref), several times/wk + every day	Total, lung, stomach, colorectal, pancreatic	M: 1, 5 F: 1, 5, 31, 32, 33	12

(*Continued*)

TABLE 1 (*Continued*)

First author, year	Country	Cohort name	Follow-up period	Age at baseline, y	Participants	No. of deaths	Exposure category	Cancer type	Adjustment for covariates[2]	NOS score
Sakauchi, 2004 (37)	Japan	The Japan Collaborative Cohort	9.8 y	≥40	114,517	88	Milk ≤1–2/mo (ref), 1–4/wk, almost every day Yogurt Seldom, 1–2/mo, ≥1–2/wk Cheese Seldom, 1–2/mo, ≥1–2/wk Butter Seldom, 1–2/mo, ≥1–2/wk	Urothelial	1, 2, 5	10
Koh, 2006 (38)	United States	The Harvard Alumni Health Study	11 y	67	10,011	99	Dairy 0–<1.25 (ref), 1.25–<2.00, 2.00–<3.25, ≥3.25 servings/d	Prostate	1, 4, 5, 6, 7, 8, 12, 17, 25	12
Sakauchi, 2007 (40)	Japan	The Japan Collaborative Cohort	13.3 y	40–79	64,327	77	Milk ≤1–2 times/mo (ref), 1–4 times/wk, almost every day Yogurt Seldom (ref), 1–2 times/mo, ≥1–2 times/wk Cheese Seldom (ref), 1–2 times/mo, ≥1–2 times/wk Butter Seldom (ref), 1–2 times/mo, ≥1–2 times/wk	Ovarian	1, 4, 8, 9, 34, 35, 36	12
Park, 2007 (12)	United States	The NIH-AARP Diet and Health Study	6 y	50–71	293,888	178	Dairy <0.5 (ref), 0.5–<1, 1–<2, 2–<3, ≥3 servings/d Whole milk 0 (ref), >0–<0.5, 0.5–<1, 1–<2, ≥2 servings/d Low-fat milk 0 (ref), >0–<0.5, 0.5–<1, 1–<2, ≥2 servings/d Skim milk 0 (ref), >0–<0.5, 0.5–<1, 1–<2, ≥2 servings/d Yogurt 0 (ref), >0–<0.5, ≥0.5 servings/d Cheese <0.1 (ref), 0.1–<0.25, 0.25–<0.5, 0.5–<0.75, ≥0.75 servings/d	Prostate	1, 3, 4, 5, 6, 7, 8, 9, 12, 17, 25, 37, 38, 39, 40, 41, 42	10
Matsumoto, 2007 (39)	Japan	The Jichi Medical School Cohort Study	9.15 y	18–90	11,606	255	Milk Not every day (ref), every day Yogurt Not every day (ref), every day Butter Not every day (ref), every day	Total, colon, stomach, lung, liver, pancreas, bile duct	1, 2	9

(*Continued*)

TABLE 1 (*Continued*)

First author, year	Country	Cohort name	Follow-up period	Age at baseline, y	Participants	No. of deaths	Exposure category	Cancer type	Adjustment for covariates[2]	NOS score
Smit, 2007 (41)	United States	The Puerto Rico Heart Health Program	41 y	35–79	9824	167	Dairy ≤2 (ref), 3–4, 5–6, ≥7 servings/d	Prostate	1, 4, 5, 6, 8, 9, 30	12
Bonthuis, 2010 (42)	Australia		14.4 y	25–78	1529	58	Dairy Lowest (ref), highest	Total	1, 2, 4, 5, 6, 7, 8, 9, 43, 44	12
Sharma, 2013 (43)	United States	The Multiethnic Cohort study	9 y	45–75	146,389	3546	Dairy M: 0.5 (ref), 0.6–1.0, 1.1–1.7, >1.7 servings/d F: 0.5 (ref), 0.6–1.0, 1.1–1.6, >1.6 servings/d	Total	1, 4, 5, 6, 7, 8, 9, 36, 38	10
Song, 2013 (13)	United States	The Physicians' Health Study	28 y	40–84	21,660	305	Dairy ≤0.5 (ref), >0.5–1.0, >1.0–1.5, >1.5–2.5, >2.5 servings/d Whole milk Rarely (ref), ≤1 serving/wk, 2–6 servings/wk, ≥1 serving/d Skim/low-fat milk Rarely (ref), ≤1 serving/wk, 2–6 servings/wk, ≥1 serving/d	Prostate	1, 3, 4, 5, 6, 7, 8, 17, 18, 44, 45, 46	11
Michaelsson, 2014 (45)	Sweden	Swedish Mammography Cohort	20.1 y	39–74	61,443	3283	Milk <200 (ref), 200–399, 400–599, ≥600 g/d Soured milk and yogurt <1 (ref), 1–199, 200–399, ≥400 g/d Cheese <20 (ref), 20–39, 40–59, ≥60 g/d	Total	1, 4, 5, 6, 7, 8, 9, 36, 37, 41, 43, 47, 48, 49, 50, 51, 52, 53	12
Michaelsson, 2014 (45)	Sweden	Cohort of Swedish Men	11.2 y	45–79	45,339	2881	Milk <200 (ref), 200–399, 400–599, ≥600 g/d Soured milk and yogurt <1 (ref), 1–199, 200–399, ≥400 g/d Cheese <20 (ref), 20–39, 40–59, ≥60 g/d	Total	1, 4, 5, 6, 7, 8, 9, 37, 41, 43, 47, 48, 49, 50,51, 52, 53	12
Huang, 2014 (44)	Taiwan	The Nutrition and Health Survey in Taiwan	13.7 y	19–64	3810	145	Dairy 0 (ref), 0.1–3.0, 3.1–7.0, >7.0 times/wk	Total	1, 2, 3, 4, 9, 30, 37, 38, 48	10
Wang, 2015 (47)	Japan	Japan Collaborative Cohort study	19 y	40–79	94,980	7688	Milk Never (ref), 1–2 times/mo, 1–2 times/wk, 3–4 times/wk, almost every day	Total	1, 4, 5, 7, 8, 9, 25, 31, 38, 54	12

(*Continued*)

TABLE 1 (*Continued*)

First author, year	Country	Cohort name	Follow-up period	Age at baseline, y	Participants	No. of deaths	Exposure category	Cancer type	Adjustment for covariates[2]	NOS score
Praagman, 2015 (46)	Netherlands	European Prospective Investigation into Cancer and Nutrition-Netherlands cohort	15 y	20–70	34,409	1216	Yogurt 3.8 (ref), 26.6, 62.9, 144.5 g/d Cheese 15.8 (ref), 26.8, 29.2, 30.2 g/d	Total	1, 2, 4, 5, 6, 7, 8, 9, 25, 45, 55	12
Farvid, 2017 (48)	Iran	The Golestan Cohort Study	11 y	36–83	42,403	859	Dairy 0.4 (ref), 0.8, 1.2, 1.6, 2.4 servings/d High-fat dairy 0 (ref), 0.05, 0.2, 0.5, 1.1 servings/d Low-fat dairy 0.2 (ref), 0.5, 0.8, 1.0, 1.6 servings/d Milk 0 (ref), 0.04, 0.1, 0.3, 0.6 servings/d Yogurt 0.1 (ref), 0.3, 0.4, 0.6, 0.9 servings/d Cheese 0 (ref), 0.1, 0.3, 0.5, 0.8 servings/d	Total	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 30, 37, 46, 56	13
Um, 2017 (14)	United States	Reasons for Geographic and Racial Differences in Stroke study	10 y	≥45	21,427	854	Dairy M: 0–<46.8 (ref), 46.8–<116, 116–<206, 206–<350, 350–1468 g/d F: 0–<37.1 (ref), 37.1–<93.8, 93.8–<177, 177–<319, 319–1368 g/d Whole milk M: 0 (ref), >0–<34.8, 34.8–<112, 112–<246, 246–1216 g/d F: 0 (ref), >0–<20.9, 20.9–<78.0, 78.0–<186, 186–1288 g/d Low-fat milk M: 0 (ref), >0–<39.4, 39.4–<121, 121–<249, 249–1310 g/d F: 0 (ref), >0–<23.7, 23.7–<97.3, 97.3–<230, 230–1351 g/d Nonfat milk M: 0 (ref), >0–<109, 109–<239, 239–<383, 383–1220 g/d F: 0 (ref), >0–<105, 105–<208, 208–<382, 382–1175 g/d	Total	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 17, 25, 30, 36, 43, 46, 48, 55	12
Bergholdt, 2018 (49)	Denmark	The Copenhagen General Population Study	7 y	57	74,243	1668	Milk No milk (ref), 1–3, 4–7, 8–10, ≥11 glasses/wk	Total	1, 2, 4, 5, 7, 8, 9, 10, 17, 22, 25,37, 40, 46, 55, 57, 58, 59, 60, 61	10

(*Continued*)

TABLE 1 (*Continued*)

First author, year	Country	Cohort name	Follow-up period	Age at baseline, y	Participants	No. of deaths	Exposure category	Cancer type	Adjustment for covariates[2]	NOS score
Um, 2019 (51)	United States	Iowa Women's Health Study	27 y	55–69	35,221	4665	Dairy 0–7.5 (ref), >7.5–11.8, >11.8–18.0, >18.0–24.5, >24.5–143 servings/wk High-fat dairy 0–2.5 (ref), >2.5–5.0, >5.0–8.0, >8.0–13.5, >13.5–128 servings/wk Low-fat dairy 0 (ref), >0–2.0, >2.0–6.5, >6.5–14.0, >14.0–84.0 servings/wk Milk 0–0.5, >0.5–3, >3–6.5, >6.5–14, >14 servings/wk Whole milk 0 (ref), >0–0.5, >0.5–1.0, >1.0–5.5, >5.5–42 servings/wk Low-fat/nonfat milk 0 (ref), >0–1.0, >1.0–5.5, >5.5–7.0, >7.0–42.0 servings/wk	Total, colorectal	1, 4, 5, 6, 7, 8, 12, 17, 25, 36, 41, 43, 48, 55	12
Ding, 2019 (15)	United States	Nurses' Health Study, Nurses' Health Study II, and the Health Professionals Follow-up Study	32 y	25–75	217,755	15,120	Dairy 0.8 (ref), 1.5, 2, 2.8, 4.2 servings/d Whole milk <1/mo (ref), 1–3/mo, 3/mo–2/wk, ≥2/wk Skimmed or low-fat milk <1/wk (ref), 1–4/wk, 4/wk–1.5/d, ≥1.5/d Cheese <1/wk (ref), 1–4/wk, 4/wk–1.5/d, ≥1.5/d	Total, colorectal, pancreatic, lung, breast, ovarian, endometrial, prostate	1, 4, 5, 6, 7, 8, 12, 18, 34, 36, 45, 48, 57	NHS: 11 NHSII:11 HPFS: 11
Pala, 2019 (50)	Italy	European Prospective Investigation into Cancer and Nutrition (EPIC)—Italy study	14.9 y	50.1	45,009	1464	Milk 0 (ref), >0–≤50, >50–≤160, >160–≤200, >200 g/d Full-fat milk 0 (ref), >0–≤50, >50–≤160, >160–≤200, >200 g/d Reduced-fat milk 0 (ref), >0–≤50, >50–≤160, >160–≤200, >200 g/d Yogurt 0 (ref), >0–≤35, >35–≤120, >120 g/d	Total	1, 2, 5, 6, 7, 8, 18, 30, 47, 48, 62, 63, 64, 65	11

(*Continued*)

TABLE 1 (*Continued*)

First author, year	Country	Cohort name	Follow-up period	Age at baseline, y	Participants	No. of deaths	Exposure category	Cancer type	Adjustment for covariates[2]	NOS score
Mazidi, 2019 (5)	United States	National Health and Nutrition Examination Surveys study	76.4 mo	≥20	24,474	827	Cheese >0–≤28 (ref), >28–≤70, >70–≤100, >100 g/d Butter 0 (ref), >0–≤1.4, >1.4–100.1 g/d Dairy 0.25 (ref), 0.79, 1.57, 3.08 cup equivalent servings/d Milk 0.10 (ref), 0.15, 0.75, 1.84 cup equivalent servings/d	Total	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 37,45, 52, 53, 66, 67	9
van den Brandt, 2019 (52)	Netherlands	Netherlands Cohort Study	10 y	55–69	120,852	3917	Cheese Q1 (ref), Q2, Q3, Q4 Yogurt Q1 (ref), Q2, Q3, Q4 Low-fat dairy 0 (ref), 85.4, 203.3, 392.9 g/d	Total	1, 2, 4, 5, 6, 7, 8, 9, 25, 36, 38, 43, 47, 55	12
Stasinopoulos, 2020 (55)	United Kingdom	UK Biobank study	4.2 y	40–69	497,828	8297	Dairy No (ref), yes	Total	1, 2, 3, 4, 5, 7, 8, 9, 21, 30, 31, 46	10
Wang, 2020 (56)	China	The Guangzhou Biobank Cohort Study	11.5 y	≥50	19,618	1209	Dairy 0 (ref), 1, 2, >3 portions/wk Milk 0 (ref), 1–3, >3 portions/wk	Total, lung, liver, gastrointestinal, colorectal and anus, esophagus	1, 2, 4, 5, 6, 7, 8, 9, 10, 11, 31, 45	13
Schmid, 2020 (54)	United States	Nurses' Health Study and Health Professionals Follow-up Study	32 y	30–75	122,626	11,985	Yogurt Never (ref), >0 to ≤1–3 servings/mo, 1 serving/wk, 2–4 servings/wk, >4 servings/wk	Total	1, 3, 4, 5, 6, 7, 8, 12, 17, 25, 34, 36, 38, 43, 46, 47, 50, 55, 57, 67, 68, 69, 70	NHS: 11 HPFS: 11
Michels, 2020 (53)	United States	Nurses' Health Study and Health Professionals Follow-up Study	32 y	30–75	120,052	1086	Yogurt Never or <1 serving/mo (ref), 1–3 servings/mo, >1 serving/wk	Colorectal	1, 4, 5, 6, 7, 8, 12, 14, 15, 17, 34, 36, 41, 43, 46, 47, 50, 57, 67, 68	NHS: 11 HPFS: 11
Sun, 2021 (57)	United States	Women's Health Initiative	18.1 y	50–79	102,521	7516	Dairy Q1 (ref), Q2, Q3, Q4, Q5	Total	1, 3, 5, 6, 7, 8, 9, 10, 25, 36, 45, 53, 55, 57, 71, 72, 73	12

[1] F, female; M, male; NOS, Newcastle–Ottawa Scale; Q, quintile; ref, reference.

[2] Adjustment for covariates: age (1), sex (2), race/ethnicity (3), BMI (4), smoking (5), energy intake (6), alcohol intake (7), physical activity (8), education (9), income (10), occupation (11), family history of cancer (12), age at menarche (13), age at first pregnancy (14), age at menopause (15), percent desirable weight (16), meat (17), subtypes of dairy foods (18), egg (19), FEV_1 (forced expiratory volume in 1 second) (20), deprivation category (21), household (22), car user (23), bronchitis (24), vegetable (25), liver (26), oil (27), suimono (28), pickled food (29), region (30), health status (31), health education (32), health screening (33), menopausal status (34), number of pregnancies (35), hormone use (36), marital status (37), history of disease (except cancer) (38), screening for prostate cancer by use of prostate-specific antigen (39), fish (40), vitamin (41), α-linolenic acid (42), dietary supplement use (43), β-carotene treatment (44), baseline disease status (except cancer) (45), medication use (46), height (47), dietary pattern (48), Charlson's comorbidity index (49), calcium (50), phosphorus (51), fat (52), protein (53), sleeping duration (54), fruit (55), systolic blood pressure (56), family medical history (57), fast food (58), soda drinks (59), coffee (60), tea (61), weight (62), waist-to-hip ratio (63), relative index of inequality (64), sugar (65), carbohydrates (66), fiber (67), 2-y follow-up cycle (68), glycemic load (69), nuts (70), observational study/clinical trials (71), whole grain (72), and sugar-sweetened beverage (73).

TABLE 2 Pooled RRs of total cancer and cancer-specific mortality for the highest compared with lowest dairy consumption

Characteristic	Studies (*n*)	RR (95% CI)	Heterogeneity	*P*-difference
Total dairy				
All studies	13	0.99 (0.95, 1.03)	$I^2 = 24.9\%, P = 0.20$	
Sex				
Male	2	1.03 (0.94, 1.12)	$I^2 = 24.8\%, P = 0.25$	0.78
Female	5	1.02 (0.96, 1.08)	$I^2 = 23.6\%, P = 0.26$	
Cancer site				
Gastrointestinal tract	7	0.89 (0.71, 1.12)	$I^2 = 30.9\%, P = 0.22$	
Stomach	2	1.26 (0.72, 2.23)	$I^2 = 0\%, P = 0.80$	
Colorectal	5	0.83 (0.63, 1.10)	$I^2 = 54.6\%, P = 0.11$	
Pancreatic cancer	3	1.06 (0.86, 1.31)	—	0.41[1]
Lung cancer	5	0.79 (0.47, 1.32)	$I^2 = 79.5\%, P = 0.01$	0.89[1]
Women's cancer	2	1.06 (0.92, 1.23)	$I^2 = 0\%, P = 0.83$	0.27[1]
Prostate cancer	8	1.11 (0.99, 1.25)	$I^2 = 0\%, P = 0.7$	0.10[1]
Fat content				
High-fat dairy	2	0.92 (0.69, 1.23)	$I^2 = 77.8\%, P = 0.03$	0.99
Low-fat dairy	3	0.96 (0.89, 1.03)	$I^2 = 0\%, P = 0.61$	
Geographic region				
United States	8	1.02 (0.98, 1.06)	$I^2 = 0\%, P = 0.61$	
Asia	3	0.82 (0.66, 1.02)	$I^2 = 0\%, P = 0.89$	0.09[2]
Europe	1	0.91 (0.84, 0.98)	—	0.04[2]
Oceania	1	0.94 (0.42, 2.11)	—	0.85[2]
Adjustment for covariates[3]				
Strong adjustment	6	1.00 (0.94, 1.06)	$I^2 = 0\%, P = 0.60$	0.88
Weak adjustment	7	0.98 (0.92, 1.05)	$I^2 = 60.1\%, P = 0.04$	
Milk				
All studies	17	1.04 (0.99, 1.08)	$I^2 = 65.8\%, P < 0.001$	
Sex				
Male	5	1.00 (0.94, 1.07)	$I^2 = 39.1\%, P = 0.16$	0.19
Female	6	1.10 (1.01, 1.21)	$I^2 = 71.4\%, P = 0.004$	
Cancer site				
Upper digestive tract	2	1.17 (0.71, 1.94)	$I^2 = 77.9\%, P = 0.004$	
Esophageal	2	1.80 (0.53, 6.04)	$I^2 = 86.8\%, P = 0.006$	
Gastrointestinal tract	12	0.97 (0.88, 1.06)	$I^2 = 20.7\%, P = 0.20$	0.47[4]
Stomach	6	1.06 (0.80, 1.41)	$I^2 = 39.5\%, P = 0.13$	
Colorectal	9	0.96 (0.87, 1.07)	$I^2 = 21.4\%, P = 0.23$	
Hepatobiliary system	7	1.07 (1.00, 1.14)	$I^2 = 0\%, P = 0.94$	0.93[4]
Liver	3	1.13 (1.02, 1.26)	$I^2 = 0\%, P = 0.82$	
Pancreatic	6	1.06 (0.96, 1.18)	$I^2 = 0\%, P = 0.99$	
Respiratory tract	10	1.03 (0.92, 1.15)	$I^2 = 27.7\%, P = 0.17$	0.80[4]
Lung	10	1.03 (0.90, 1.17)	$I^2 = 34.4\%, P = 0.13$	
Women's cancer	5	1.13 (1.01, 1.26)	$I^2 = 35.5\%, P = 0.15$	0.56[4]
Breast	4	1.02 (0.91, 1.14)	$I^2 = 0\%, P = 0.52$	
Ovarian	4	1.32 (1.13, 1.55)	$I^2 = 0\%, P = 0.78$	
Prostate cancer	5	1.23 (1.02, 1.48)	$I^2 = 49.8\%, P = 0.09$	0.27[4]
Urological system	2	1.05 (0.52, 2.11)	$I^2 = 90.9\%, P < 0.001$	0.60[4]
Fat content[5]				
High/whole-fat milk	6	1.17 (1.07, 1.28)	$I^2 = 45.0\%, P = 0.14$	0.02
Low/skimmed milk	6	1.01 (0.96, 1.05)	$I^2 = 0\%, P = 0.40$	
Geographic region				
United States	6	1.04 (0.98, 1.09)	$I^2 = 64.1\%, P = 0.04$	
Asia	6	1.02 (0.95, 1.09)	$I^2 = 60.2\%, P = 0.01$	0.73[6]
Europe	5	1.06 (0.90, 1.26)	$I^2 = 79.9\%, P = 0.001$	0.74[6]
Adjustment for covariates				
Strong adjustment	6	1.09 (0.97, 1.22)	$I^2 = 82.6\%, P < 0.001$	0.25
Weak adjustment	11	1.02 (0.99, 1.06)	$I^2 = 37.6\%, P = 0.10$	
Fermented milk				
All studies	10	0.95 (0.89, 1.01)	$I^2 = 45.9\%, P = 0.05$	
Sex				
Male	3	0.96 (0.80, 1.14)	$I^2 = 55.8\%, P = 0.10$	0.27
Female	3	0.85 (0.77, 0.94)	$I^2 = 0\%, P = 0.68$	
Cancer site				
Gastrointestinal tract	5	0.91 (0.79, 1.04)	$I^2 = 0\%, P = 0.59$	
Stomach	2	1.34 (0.67, 2.69)	$I^2 = 0\%, P = 0.45$	
Colorectal	5	0.89 (0.78, 1.03)	$I^2 = 0\%, P = 0.59$	

(*Continued*)

TABLE 2 (*Continued*)

Characteristic	Studies (*n*)	RR (95% CI)	Heterogeneity	*P*-difference
Hepatobiliary system	2	1.16 (0.50, 2.72)	$I^2 = 0\%$, $P = 0.56$	0.58[7]
Pancreatic	2	0.81 (0.29, 2.22)	$I^2 = 0\%$, $P = 0.82$	
Lung cancer	3	0.87 (0.65, 1.17)	$I^2 = 0\%$, $P = 0.82$	0.80[7]
Ovarian cancer	1	1.66 (0.71, 3.90)	—	0.19[7]
Prostate cancer	1	0.78 (0.25, 2.47)	—	0.80[7]
Urothelial cancer	1	0.72 (0.33, 1.57)	—	0.57[7]
Geographic region				
United States	3	0.98 (0.88, 1.08)	$I^2 = 71.2\%$, $P = 0.03$	
Asia	3	0.85 (0.71, 1.03)	$I^2 = 0\%$, $P = 0.60$	0.50[8]
Europe	4	0.93 (0.85, 1.02)	$I^2 = 20.6\%$, $P = 0.29$	0.27[8]
Adjustment for covariates				
Strong adjustment	5	0.94 (0.87, 1.02)	$I^2 = 54.0\%$, $P = 0.07$	0.82
Weak adjustment	5	0.95 (0.84, 1.08)	$I^2 = 36.8\%$, $P = 0.16$	
Cheese				
All studies	10	0.99 (0.98, 1.01)	$I^2 = 0\%$, $P = 0.79$	
Sex				
Male	3	1.00 (0.89, 1.12)	$I^2 = 13.9\%$, $P = 0.31$	0.63
Female	4	1.04 (0.95, 1.14)	$I^2 = 0.3\%$, $P = 0.39$	
Cancer site				
Gastrointestinal tract	6	1.22 (1.02, 1.45)	$I^2 = 0\%$, $P = 0.85$	
Colorectal	6	1.22 (1.02, 1.46)	$I^2 = 0\%$, $P = 0.66$	
Pancreatic cancer	4	1.25 (0.89, 1.76)	$I^2 = 0\%$, $P = 0.69$	0.89[9]
Lung cancer	6	0.85 (0.63, 1.15)	$I^2 = 41.5\%$, $P = 0.13$	0.03[9]
Women's cancer	4	1.15 (0.93, 1.44)	$I^2 = 0\%$, $P = 0.86$	0.72[9]
Breast	3	1.16 (0.88, 1.53)	$I^2 = 0\%$, $P = 0.63$	
Ovarian	3	1.24 (0.81, 1.90)	$I^2 = 0\%$, $P = 0.50$	
Prostate cancer	3	1.17 (0.89, 1.55)	$I^2 = 0\%$, $P = 0.53$	0.84[9]
Urothelial cancer	1	0.91 (0.68, 1.21)	—	0.11[9]
Geographic region				
United States	4	0.99 (0.97, 1.01)	$I^2 = 0\%$, $P = 0.45$	
Asia	2	1.00 (0.80, 1.24)	$I^2 = 0\%$, $P = 0.95$	0.96[10]
Europe	4	1.04 (0.96, 1.13)	$I^2 = 0\%$, $P = 0.47$	0.27[10]
Adjustment for covariates				
Strong adjustment	5	0.99 (0.97, 1.01)	$I^2 = 0\%$, $P = 0.49$	0.35
Weak adjustment	5	1.04 (0.95, 1.14)	$I^2 = 0\%$, $P = 0.97$	

[1] *P* value for difference in RRs of total dairy consumption for hepatobiliary system compared with gastrointestinal tract, lung cancer compared with gastrointestinal tract, women's cancer compared with gastrointestinal tract, and prostate cancer compared with gastrointestinal tract.
[2] *P* value for difference in RRs of total dairy consumption for Asia compared with United States, Europe compared with United States, and Oceania compared with United States.
[3] Adjustment for at least age, BMI, energy intake, alcohol intake, smoking status, physical activity, and socioeconomic status is considered strong adjustment. Otherwise, it is considered weak adjustment.
[4] *P* value for difference in RRs of milk consumption for gastrointestinal tract compared with upper digestive tract, hepatobiliary system compared with upper digestive tract, respiratory tract compared with upper digestive tract, women's cancer compared with upper digestive tract, prostate cancer compared with upper digestive tract, and urological system compared with upper digestive tract.
[5] Milk fat content ≥3.5% was defined as high/whole-fat milk, and milk fat content <3.5% was defined as low-fat milk.
[6] *P* value for difference in RRs of milk consumption for Asia compared with United States and Europe compared with United States.
[7] *P* value for difference in RRs of fermented milk consumption for hepatobiliary system compared with gastrointestinal tract, lung cancer compared with gastrointestinal tract, ovarian cancer compared with gastrointestinal tract, prostate cancer compared with gastrointestinal tract, and urothelial cancer compared with gastrointestinal tract.
[8] *P* value for difference in RRs of fermented milk consumption for Asia compared with United States and Europe compared with United States.
[9] *P* value for difference in RRs of cheese consumption for pancreatic cancer compared with gastrointestinal tract, lung cancer compared with gastrointestinal tract, women's cancer compared with gastrointestinal tract, prostate cancer compared with gastrointestinal tract, and urothelial cancer compared with gastrointestinal tract.
[10] *P* value for difference in RRs of cheese consumption for Asia compared with United States and Europe compared with United States.

was 1.04 (95% CI: 0.99, 1.08) with significant heterogeneity among the studies ($I^2 = 65.8\%$, $P < 0.001$) (Table 2, **Figure 3**). The increased risk of total cancer mortality was observed in females (RR: 1.10; 95% CI: 1.01, 1.21) but not in males (RR: 1.00; 95% CI: 0.94, 1.07; *P*-difference = 0.19). By cancer site, significant associations were detected in cancers of the hepatobiliary system (RR: 1.07; 95% CI: 1.00, 1.14), women's cancer (RR: 1.13; 95% CI: 1.01, 1.26), and prostate cancer (RR: 1.23; 95% CI: 1.02, 1.48) but not in cancers of the upper digestive tract, gastrointestinal tract, respiratory tract, and urological system. For cancers of the hepatobiliary system, high milk consumption was associated with increased mortality risk from liver cancer (RR: 1.13; 95% CI: 1.02, 1.26), but no significant association was detected in pancreatic cancer (RR: 1.06; 95% CI: 0.96, 1.18). For women's cancer, high milk consumption was associated with increased mortality risk from ovarian cancer (RR: 1.32; 95% CI: 1.13, 1.55), but no significant association was detected

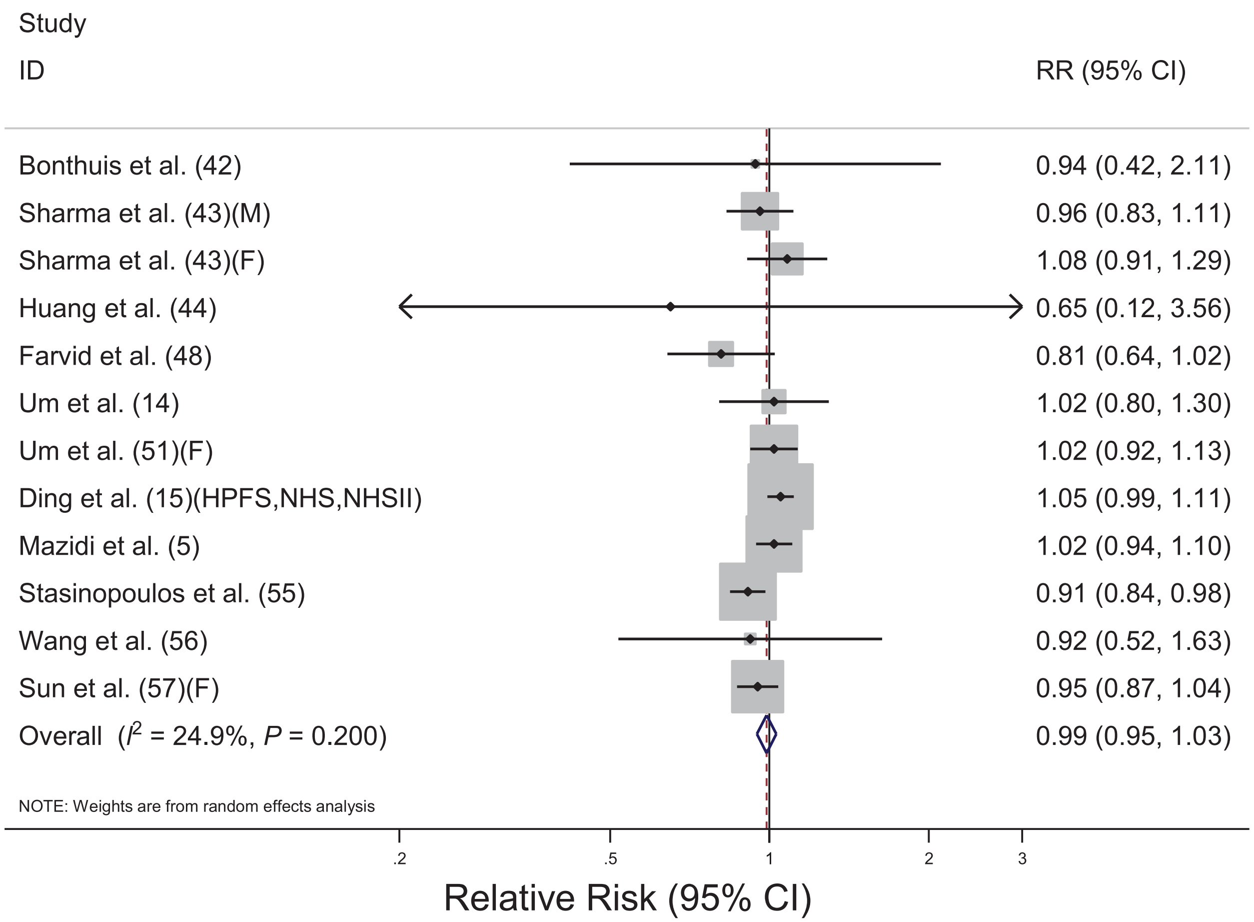

FIGURE 2 Forest plot of total cancer mortality for the highest compared with lowest categories of total dairy consumption. The sizes of the squares correspond to the inverse of the variance of the natural logarithm of the RR from the individual study, and the diamond indicates the pooled RR. F, female; HPFS, Health Professionals Follow-up Study; M, male; NHS, Nurses' Health Study; NHSII, Nurses' Health Study II.

in breast cancer (RR: 1.02; 95% CI: 0.91, 1.14). However, pooled RRs were not significantly different with cancer sites in the meta-regression analysis (P-difference > 0.2 for all comparisons). High/whole-fat milk intake was associated with an increased risk of total mortality (RR: 1.17; 95% CI: 1.07, 1.28) but not low-fat milk consumption (RR: 1.01; 95% CI: 0.96, 1.05), and there was a significant difference in fat content (P-difference = 0.02). There was no significant difference in the geographic region or adjustment factors based on meta-regression analyses results (P-difference > 0.2 for all comparisons). The dose-response analysis for milk consumption and total cancer mortality included 13 studies (10, 14, 15, 45, 47–51, 56) (Table 3). The pooled RR for an increase in milk consumption of 200 g/d was 1.01 (95% CI: 0.99, 1.04). By sex, a 200-g/d increment of milk consumption was associated with a 4% increase in cancer mortality in females (RR: 1.04; 95% CI: 1.01, 1.06), whereas there was no significant association in males (RR: 0.99; 95% CI: 0.97, 1.02). By fat content, a 200-g/d increment of high/whole-fat milk consumption was associated with 12% increase in total cancer mortality (RR: 1.12; 95% CI: 1.01, 1.23) but not low-fat milk consumption (RR: 1.00; 95% CI: 0.99, 1.02).

Fermented milk consumption and cancer mortality

The association between fermented milk consumption and total cancer mortality was evaluated in 10 prospective cohort studies, including 390,467 participants and 23,014 deaths. The pooled RR for highest compared with lowest consumption was 0.95 (95% CI: 0.89, 1.01) with evidence of moderate heterogeneity (I^2 = 45.9%, P = 0.05) (Table 2, **Figure 4**). By sex, high fermented milk consumption was inversely associated with total cancer mortality in females (RR: 0.85; 95% CI: 0.77, 0.94) but not in males (RR: 0.96; 95% CI: 0.80, 1.14). The pooled RRs, however, were not significantly different by sex (P-difference = 0.27). We discovered no significant difference in cancer mortality by cancer site, geographic region, or adjustment factors. The dose-response analysis for fermented milk consumption and total cancer mortality included 7 studies (45, 46, 48, 50, 54) (Table 3). A 200-g/d increment of fermented milk consumption was

TABLE 3 Pooled RRs of dairy consumption and total cancer mortality from dose-response meta-analyses

Characteristic	Studies (*n*)	Dose, g/d	RR (95% CI)	Heterogeneity
Total dairy	10	400	1.00 (0.97, 1.04)	$I^2 = 73.8\%$, $P < 0.001$
Sex				
Male	1	400	1.07 (1.00, 1.14)	—
Female	4	400	1.02 (0.98, 1.08)	$I^2 = 72.9\%$, $P = 0.01$
Fat content				
High-fat dairy	2	400	0.94 (0.74, 1.18)	$I^2 = 46.6\%$, $P = 0.17$
Low-fat dairy	3	400	1.01 (0.98, 1.03)	$I^2 = 0\%$, $P = 0.69$
Milk	13	200	1.01 (0.99, 1.04)	$I^2 = 63.0\%$, $P = 0.002$
Sex				
Male	4	200	0.99 (0.97, 1.02)	$I^2 = 32.4\%$, $P = 0.22$
Female	5	200	1.04 (1.01–1.06)	$I^2 = 49.1\%$, $P = 0.10$
Fat content[1]				
High/whole-fat milk	6	200	1.12 (1.01, 1.23)	$I^2 = 76.9\%$, $P = 0.005$
Low-fat milk	6	200	1.00 (0.99, 1.02)	$I^2 = 0\%$, $P = 0.70$
Fermented milk	7	200	0.94 (0.90, 0.99)	$I^2 = 35.5\%$, $P = 0.16$
Sex				
Male	2	200	0.97 (0.93, 1.01)	$I^2 = 0\%$, $P = 0.36$
Female	2	200	0.90 (0.85, 0.94)	$I^2 = 0\%$, $P = 0.77$
Cheese	8	50	1.01 (0.95, 1.07)	$I^2 = 36.3\%$, $P = 0.16$
Sex				
Male	2	50	0.99 (0.90, 1.08)	$I^2 = 34.8\%$, $P = 0.22$
Female	3	50	1.05 (0.86, 1.29)	$I^2 = 83.4\%$, $P = 0.002$

[1] Milk fat content ≥3.5% was defined as high/whole-fat milk, and milk fat content <3.5% was defined as low-fat milk.

associated with a 6% decrease in total cancer mortality (RR: 0.94; 95% CI: 0.90, 0.99) with no significant heterogeneity ($I^2 = 35.5\%$, $P = 0.16$). Similarly, we discovered that increasing fermented milk consumption by 200 g/d was associated with a 10% decrease in total cancer mortality in females (RR: 0.90; 95% CI: 0.85, 0.94), whereas no association was found in males (RR: 0.97; 95% CI: 0.93, 1.01).

Cheese consumption and cancer mortality

The association between cheese consumption and total cancer mortality was evaluated in 10 prospective cohort studies including 473,990 participants and 25,894 deaths. The pooled RR for highest compared with lowest consumption was 0.99 (95% CI: 0.98, 1.01) with no heterogeneity among the studies ($I^2 = 0\%$, $P = 0.79$) (Table 2, **Figure 5**). By the cancer site, high cheese consumption was associated with an increased risk of death from colorectal cancer (RR: 1.22; 95% CI: 1.02, 1.46), but no other cancer sites showed a significant association. For lung cancer mortality, the pooled RR was 0.85 (95% CI: 0.63, 1.15), which was significantly different from colorectal cancer mortality (P-difference = 0.03). There was no significant difference in cancer mortality when stratified by sex, geographic region, or adjustment factors. Eight studies (15, 45, 46, 48, 50) were included in the dose-response analysis for cheese consumption and total cancer mortality (Table 3). The pooled RR for 50 g/d increment of cheese consumption was 1.01 (95% CI: 0.95, 1.07), showing no significant association in males and females.

Butter consumption and cancer mortality

The association between butter consumption and total cancer mortality was evaluated in 2 studies including 56,615 participants and 1719 deaths. The pooled RR for all studies was 1.06 (95% CI: 0.70, 1.59) with evidence of moderate heterogeneity ($I^2 = 65.8\%$, $P = 0.09$) (data not shown). Similarly, by cancer site, we detected no significant association in cancer of the gastrointestinal tract (RR: 1.06; 95% CI: 0.81, 1.39), hepatobiliary system (RR: 1.47; 95% CI, 0.34, 6.31), lung cancer (RR: 0.97; 95% CI: 0.73, 1.30), ovarian cancer (RR: 1.35; 95% CI: 0.56, 3.25), or urothelial cancer (RR: 0.66; 95% CI: 0.30, 1.45), and the meta-regression analysis result showed no significant differences (P-difference > 0.2 for all comparisons).

Publication bias

Begg ($P > 0.5$ in all analyses) and Egger tests ($P > 0.09$ in all analyses) of cancer mortality for total dairy, milk, fermented milk, and cheese consumption indicated no evidence of publication bias.

Discussion

The potential associations between different types of dairy products consumption and total cancer mortality or cancer-specific mortality were examined in the current meta-analysis of 34 prospective cohort studies. Compared with low consumption, high milk consumption was associated with higher total cancer mortality in females. Conversely, females in the highest category of fermented milk intake had decreased risk of cancer mortality. The dose-response meta-analysis also supports the associations. There was no

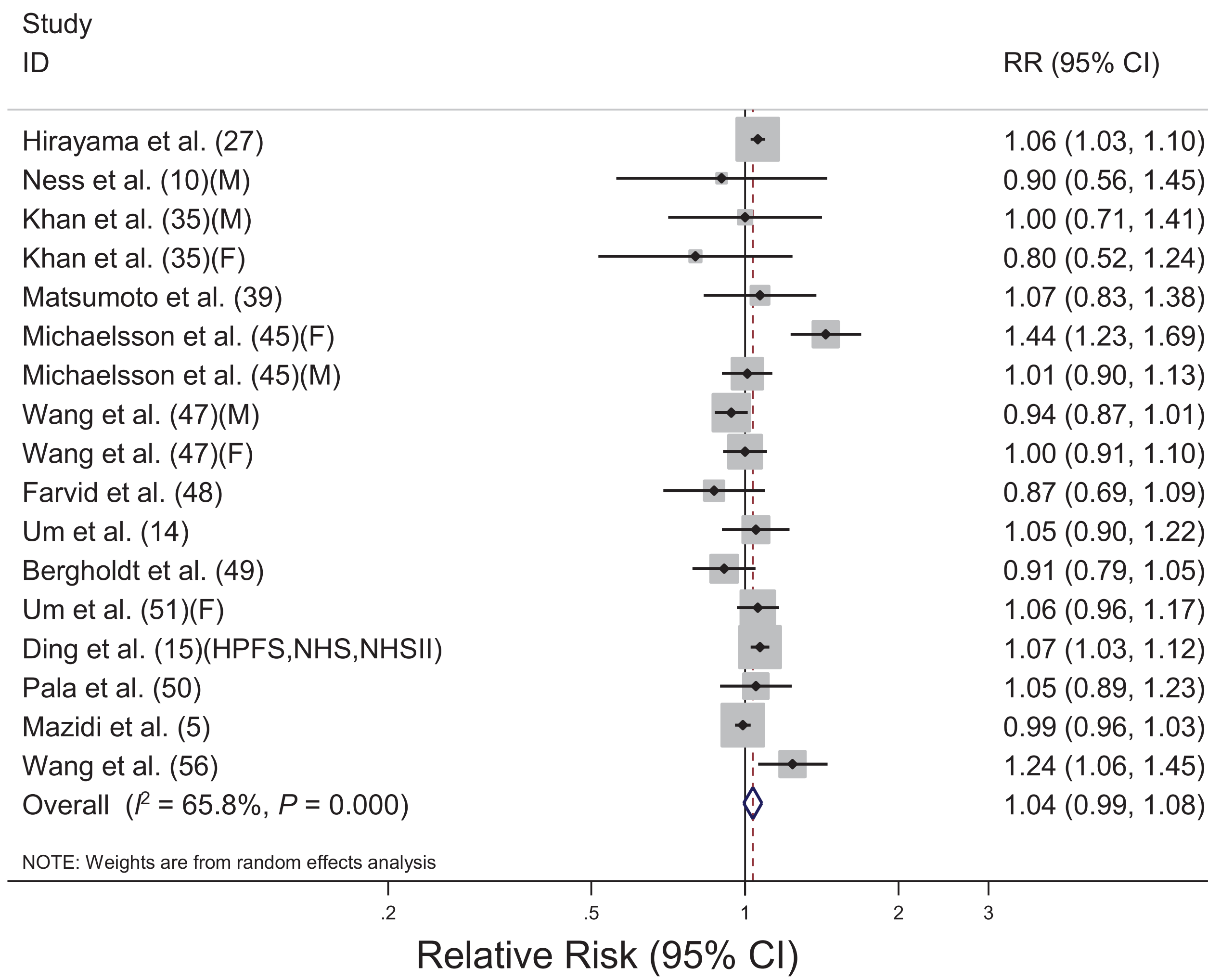

FIGURE 3 Forest plot of total cancer mortality for the highest compared with lowest categories of milk consumption. The sizes of the squares correspond to the inverse of the variance of the natural logarithm of the RR from the individual study, and the diamond indicates the pooled RR. F, female; HPFS, Health Professionals Follow-up Study; M, male; NHS, Nurses' Health Study; NHSII, Nurses' Health Study II.

significant association between cheese consumption and total cancer mortality, but we discovered an increased risk of colorectal cancer mortality in people with high cheese consumption. There was no significant association between butter consumption or total dairy consumption and cancer mortality.

Three previous meta-analyses have been conducted on the association of total cancer mortality for highest compared with lowest consumption of dairy products (4–6), and a meta-analyses only included studies reported in the United States (5). There was no significant association between total dairy consumption and total cancer mortality in the meta-analyses, which were similar to the results of total dairy consumption in this study. For milk consumption, 2 previous meta-analyses on the association between milk consumption and total cancer mortality showed no significant association (4, 6). However, in the current meta-analysis, we discovered a significant positive association between milk consumption and total cancer mortality in females. In addition, we discovered that the consumption of high/whole-fat milk but not low-fat milk was associated with an increased cancer mortality risk, and our findings were consistent with the results of Naghshi et al. (6). Only 1 previous meta-analysis was conducted to examine the association between fermented milk consumption and total cancer mortality, and it reported no association (4). In this study, we discovered a significant inverse association between fermented milk consumption and cancer mortality. Moreover, all of the previous meta-analyses included the results of all cancer mortality and cancer-specific mortality from individual studies to calculate a pooled RR of total cancer mortality, whereas we included studies that only reported all cancer mortality for the main analysis.

In this study, we discovered that milk consumption was associated with increased cancer mortality in females. The milk consumption elevated circulating concentrations of insulin-like growth factor 1 (IGF-1) (58), and previous studies indicated high IGF-1 concentrations were associated

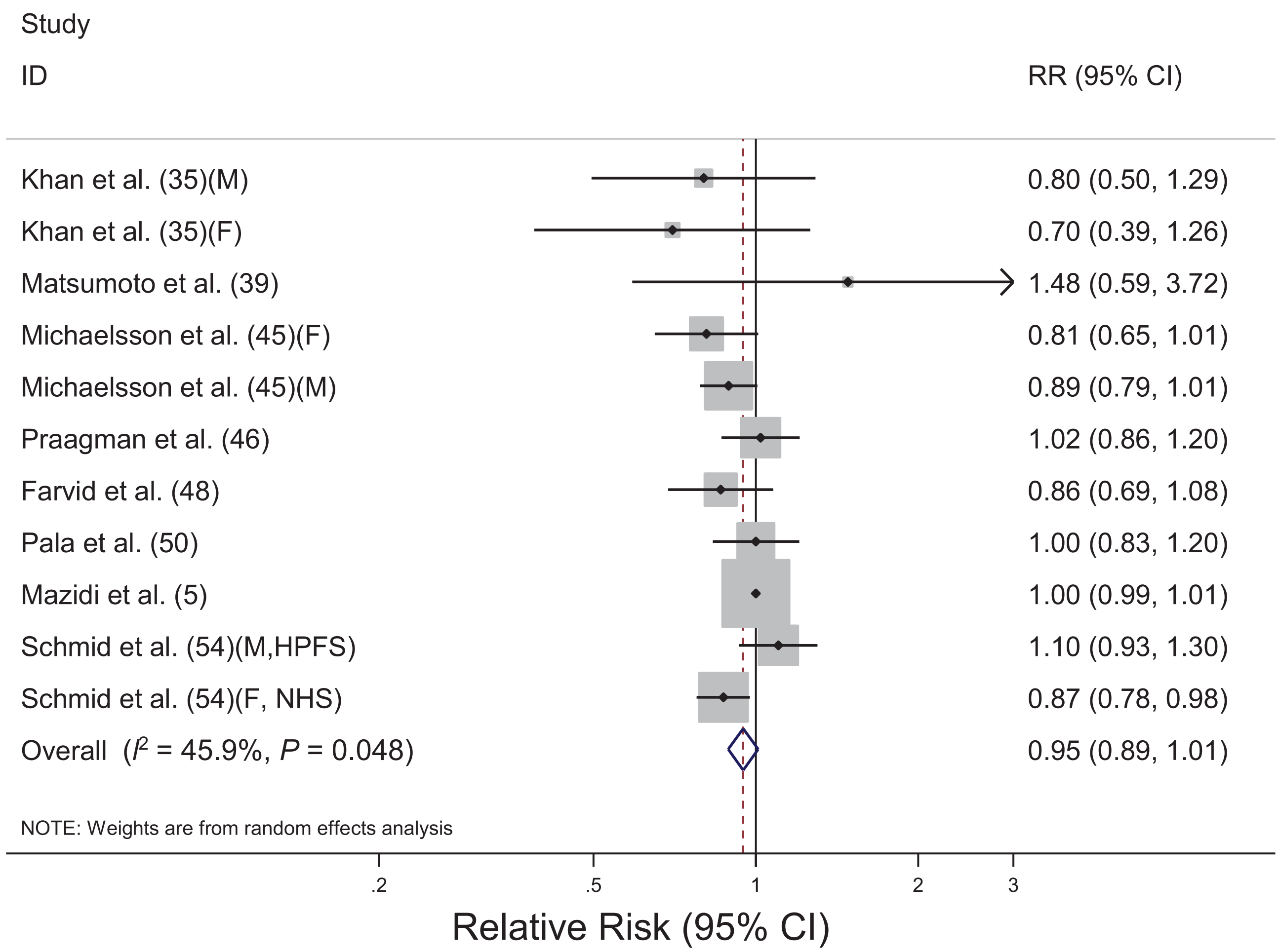

FIGURE 4 Forest plot of total cancer mortality for the highest compared with lowest categories of fermented milk consumption. The sizes of the squares correspond to the inverse of the variance of the natural logarithm of the RR from the individual study, and the diamond indicates the pooled RR. F, female; HPFS, Health Professionals Follow-up Study; M, male; NHS, Nurses' Health Study.

with increased risk of cancer, particularly breast and prostate cancer (59–61). Another previous study reported that IGF-1 could enhance the growth and metastasis of hepatocellular carcinoma (62). Furthermore, multiple large prospective cohort studies revealed that dairy products consumption was associated with a higher risk of hepatocellular carcinoma (63, 64). Milk consumption was significantly associated with an increased risk of prostate and liver cancer mortality. In addition, this positive association has also been found in women's cancer. A previous meta-analysis of ovarian cancer risk indicated that high milk and lactose intake was associated with increased ovarian cancer risk (65). In the current meta-analysis, we observed a similar positive association between milk consumption and ovarian cancer mortality. Milk contained 4.5–5.5% lactose and 227 mg free galactose per 100 mL (66). Several studies have supported the relation between lactose and free galactose consumption and increased risk of ovarian cancer (65, 66). The accumulation of galactose and galactose metabolites, such as galactose-1-phosphate and galactitol, may interfere with gonadotropin signaling and ovarian apoptosis, resulting in galactose-induced ovarian toxicity (66, 67). However, there was no significant association between women's cancer with fermented milk or cheese consumption in this study. This result could be attributed to the fact that fermented milk and cheese have significantly less lactose and total galactose than milk (67, 68). Furthermore, we discovered high/whole-fat milk consumption was associated with a higher risk of total cancer mortality. The previous meta-analysis indicated that diets high in saturated fat were associated with higher cancer mortality (69), and another study showed that whole milk consumption was associated with higher ovarian cancer risk but not for low-fat milk, yogurt, and cheese intake (67). Moreover, although a meta-analysis of milk consumption and total cancer mortality indicated evidence of heterogeneity among studies, the observed heterogeneity tended to disappear when stratified by cancer site.

We observed that fermented milk consumption was associated with a decreased risk of total cancer mortality. Fermented milk differs from other dairy products in that

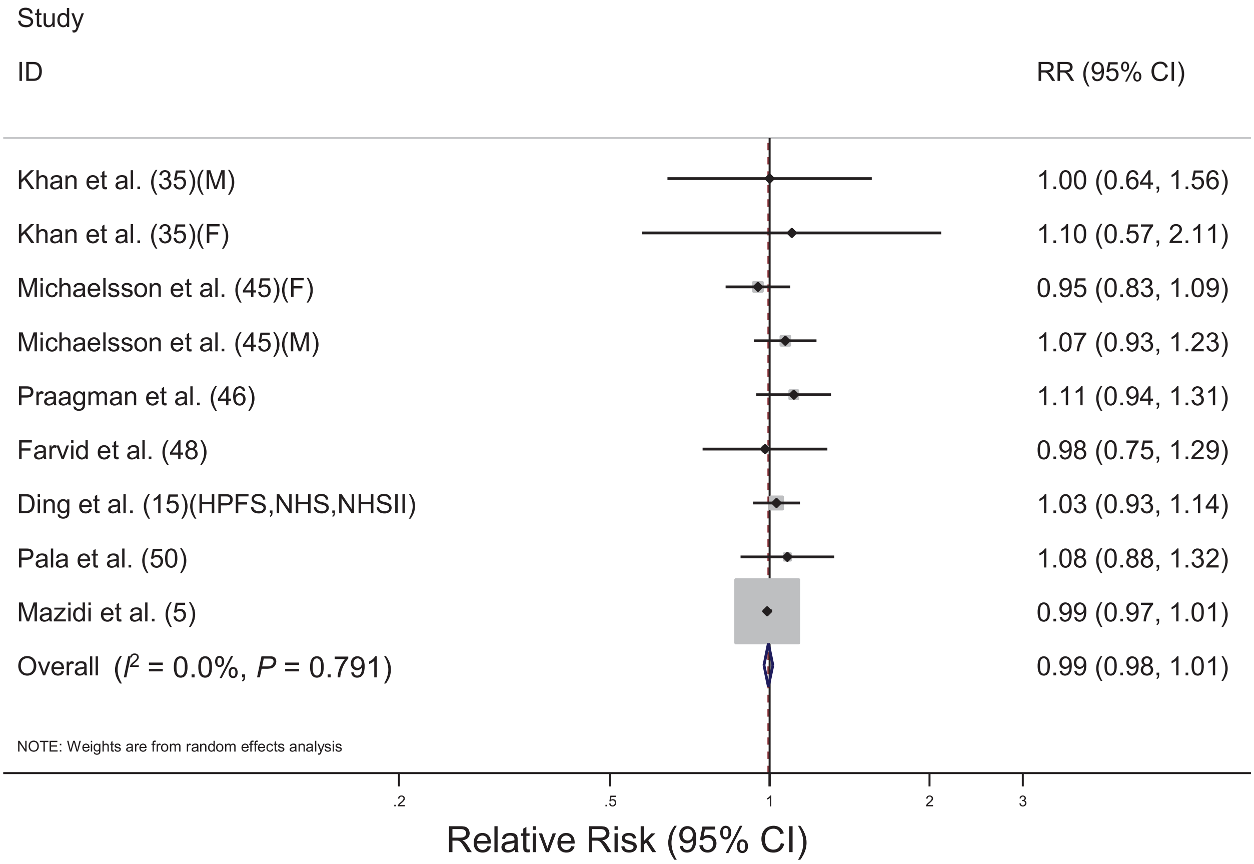

FIGURE 5 Forest plot of total cancer mortality for the highest compared with lowest categories of cheese consumption. The sizes of the squares correspond to the inverse of the variance of the natural logarithm of the RR from the individual study, and the diamond indicates the pooled RR. F, female; HPFS, Health Professionals Follow-up Study; M, male; NHS, Nurses' Health Study; NHSII, Nurses' Health Study II.

it has a high concentration of probiotic bacteria. Yogurt can increase IgA, T cells, and macrophages activities, which inhibit pathogenic microbiota growth, reducing infection and improving anticarcinogenic effects (54, 70). Schmid et al. (54) indicated that yogurt consumption might have different effects on the intestinal microbiota of males and females, and the commensal microbial community may alter sex hormone concentration. For cheese consumption, we discovered that cheese consumption was associated with a higher risk of colorectal cancer mortality. Our previous meta-analysis found no significant association between cheese consumption and colorectal cancer mortality, but the meta-analysis included only 3 prospective studies on cheese consumption (71). The recent analysis included 6 prospective studies, which were supplemented with more current data.

There are several advantages to this meta-analysis. First, to the best of our knowledge, this is the most comprehensive meta-analysis to examine the association between dairy consumption and overall cancer-specific mortality. Although previous meta-analyses of dairy consumption and cancer-specific mortality have been performed, few studies have conducted this analysis and analyzed only one cancer type, such as prostate cancer (72), lung cancer (73), and colorectal cancer (71) mortality. Second, to calculate the pooled RR for total cancer mortality, we only considered studies that reported mortality from all cancers. To calculate the pooled RR, the previous meta-analyses included studies reporting total cancer or cancer-specific mortality (4–6). Third, we added more recent studies and included the largest number of participants and cancer deaths. Due to numerous studies included, we observed several associations between each type of dairy product consumption and cancer mortality, which were not observed in the previous meta-analyses. Fourth, we assessed several dairy products that were individually stratified by sex, cancer site, fat content, and geographical region, especially its first subgroup analysis for the fermented milk and cheese consumption. Fifth, we conducted a linear dose-response meta-analysis between total dairy and each type of dairy product consumption and cancer mortality, with further stratified analysis by sex and fat content.

Despite these advantages, this meta-analysis has several limitations. First, this study was based on observational studies, and the unmeasured or residual confounding cannot be completely solved. However, most of the studies included in the meta-analysis provided estimates that were adjusted for various cancer mortality risk factors, and we further performed a stratified analysis to examine the effects of potential confounding factors. Second, measurement errors could occur when recording information during the assessment because most of the studies included in this meta-analysis employed self-reported questionnaires to estimate the dairy product intake. However, some nondifferential misclassification of dairy products intake categories may attenuate the association and likely biased the results toward the null. Third, the highest and lowest categories of dairy products consumption varied among the studies. Most studies had comparable lowest categories, such as only 1 serving size per day, but the highest category varied each study, and the highest category of most studies was open-ended. To address this limitation, we performed a dose-response analysis. Last, due to limited data, it was difficult to examine the association of dairy product consumption with cancer mortality when stratified by geographic region.

Conclusively, high milk consumption, particularly high/whole-fat milk, was associated with increased cancer mortality compared with low milk consumption, whereas high fermented milk consumption was associated with decreased cancer mortality, and this association was especially noticeable in females. Furthermore, high milk consumption was associated with increased mortality of liver cancer, ovarian cancer, and prostate cancer. Future well-designed large prospective cohort studies that investigate the association between each type of dairy product and cancer mortality in different cancer sites and populations are warranted.

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