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META-ANALYSIS

Dairy product consumption and gastric cancer risk: A meta-analysis

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Abstract

AIM: To investigate whether dairy product consumption is a risk factor for gastric cancer.

METHODS: We searched the PubMed and Web of Science databases for English-language studies on dairy product consumption and gastric cancer risk that were published between October 1980 and September 2013. One author independently extracted data and assessed study quality. Based on the heterogeneity results, we used either the fixed effects model or the random effects model to compute the summary relative risks and 95% confidence intervals (CIs). We also analyzed subgroups according to the study design, geographic region, sex, and whether there were adjustments for confounders (smoking and drinking) with respect to the sources of heterogeneity.

RESULTS: We found 39 studies that were potentially eligible for inclusion in this meta-analysis, including 10 cohort studies and 29 case-control studies. The summary relative risk for gastric cancer, comparing the highest and lowest dairy product consumption categories, was 1.06 (95%CI: 0.95-1.18). Specific analyses for milk, butter, and margarine yielded similar results, but the results for cheese and yogurt were different. There was significant heterogeneity for all studies (Q = 112.61; P = 0.000; I^2 = 67.1%). No publication bias was observed (Egger's test: P = 0.135; Begg's test: P = 0.365). There was a nonsignificant association between dairy product consumption and gastric cancer risk in the subgroup analysis for the study design, sex, geographic region, and whether there were adjustments for confounders (smoking and drinking).

CONCLUSION: In our meta-analysis, dairy product consumption was associated with a nonsignificantly increased risk of gastric cancer. However, this result should be verified using large, well-designed prospective studies.

Key words: Milk; Dairy product; Gastric cancer; Meta-analysis

Core tip: Previously published epidemiologic studies have presented inconclusive results on the association between dairy product consumption and gastric cancer risk. Therefore, we performed a meta-analysis to further explore the possibility of an association. To the best of our knowledge, this is the first meta-analysis that explores the association between dairy product consumption and gastric cancer risk. We analyzed the effects of consuming individual dairy product and the total effects of all dairy product on gastric cancer risk, and we conducted subgroup analyses for the study design, sex, region, and adjustment factors. Our study offers new insight into gastric cancer prevention.

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INTRODUCTION

Gastric cancer remains the fourth most common cancer and the second leading cause of cancer mortality worldwide, even though the incidence and mortality rates have steadily decreased over the last half century[1-3]. Epidemiological investigations have associated the risk of gastric cancer with living habits[4-6]. Because dietary intake may be an important factor in the etiology of gastric cancer[7], it has recently become popular to analyze the dietary factors that may be associated with gastric cancer.

Although milk is thought to contain all of the substances that are essential for human nutrition[8], some dairy products, such as cheese and whole milk, have a high fat content. One study associated a higher intake of high-fat dairy product with an increased risk of gastric cardia adenocarcinoma[9].

Dairy product consumption may affect various carcinogenesis pathways. Dairy intake is thought to modify cancer risk through the following biological effects: a higher circulation of insulin-like growth factor 1[10,11], modification of the vitamin D status[12,13], a higher intake of conjugated linolenic acid[14,15], and exposure to contaminants such as polychlorinated biphenyls[16-18]. Some meta-analyses have reported that dairy product consumption could increase the risk of ovarian[19] and prostate[20] cancers while reducing the risk of colorectal cancer[21,22].

It is unclear whether dairy product consumption is a risk factor for gastric cancer because the previously published epidemiologic studies have presented inconclusive results on this topic[23,24]. Therefore, we performed a meta-analysis of cohort and case-control studies to analyze the possibility of an association between dairy consumption and gastric cancer risk.

MATERIALS AND METHODS

Search strategy

We searched the PubMed (http://www.ncbi.nlm.nih.gov/pubmed/) and Web of Science (http://isiknowledge.com) databases for English-language studies on dairy product consumption and gastric cancer risk that were published between October 1980 and September 2013. We performed our search using the following terms: (dairy product or dairy or milk or food or diet) and (stomach or gastric) and (cancer or neoplasm or carcinoma or tumor).

Study selection

Studies were included if they met the following criteria: (1) had been published as an original article; (2) had a case-control or prospective cohort design; (3) had clearly defined outcomes such as gastric or stomach cancer; (4) presented relative risk (RR) estimates, odds ratios (ORs), or hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) for the association between gastric cancer and dairy product consumption; and (5) were published in English between October 1980 and September 2013. If data were duplicated in more than one study, the most recent or informative study was used. In this meta-analysis, we considered "dairy", "milk product", and "milk and dairy product" as equivalent to "dairy product."

One cohort study[25] and 21 case-control studies[9,26-45] were excluded for the following reasons: CIs were not provided[26-35], anatomic subsites or Lauren gastric cancer classifications were presented[9,25,36-38], more than one RR that involved single or multiple gastric cancer was found[39], gastric cancer was divided into two types according to the microsatellite instability status or promoter hypermethylation of the *hMLH1* gene[40,41], or the exposure was nonspecific (*e.g.*, mixed with coffee or tea)[42-45].

Data extraction

One investigator (Y.S.) extracted the following data from each publication: basic study information (first author and year of publication), the country where the study was conducted, the study design, the type of control subjects used in the case-control study (population- or hospital-based), the number of cases, the sample size, the follow-up duration, the type of dairy product and consumption categories, the RRs with 95%CIs for the association between gastric cancer and dairy product consumption, and covariate adjustments. We selected the most fully adjusted RRs for inclusion in the multivariate model.

Quality assessment

To assess the study quality, we adopted an evaluation system that was based on the Newcastle-Ottawa Scale. The quality of the included studies was evaluated based on the following three aspects: the selection of the study populations, the comparability of the populations, and the ascertainment of exposure. The highest possible score was 9 stars, and a high quality study was defined as a study with $\geqslant$ 6 stars.

Statistical analysis

The RR and its corresponding 95%CI were used to measure the effect of interest. Because gastric cancer risk is relatively low in the general population, the ORs from case-control studies were assumed to be the same as the RRs and HRs. For simplicity, we report all results as the RR[46]. One of the included case-control studies used two control groups (population- and hospital-based); we used the RR in relation to the population control subjects. We assessed the statistical heterogeneity among the studies with both the Q and I^2 statistics. The null hypothesis that the studies are homogeneous was refused if the P-value for heterogeneity was < 0.10 or the I^2 was $> 50\%$. Based on the heterogeneity results, we used either the fixed ef-

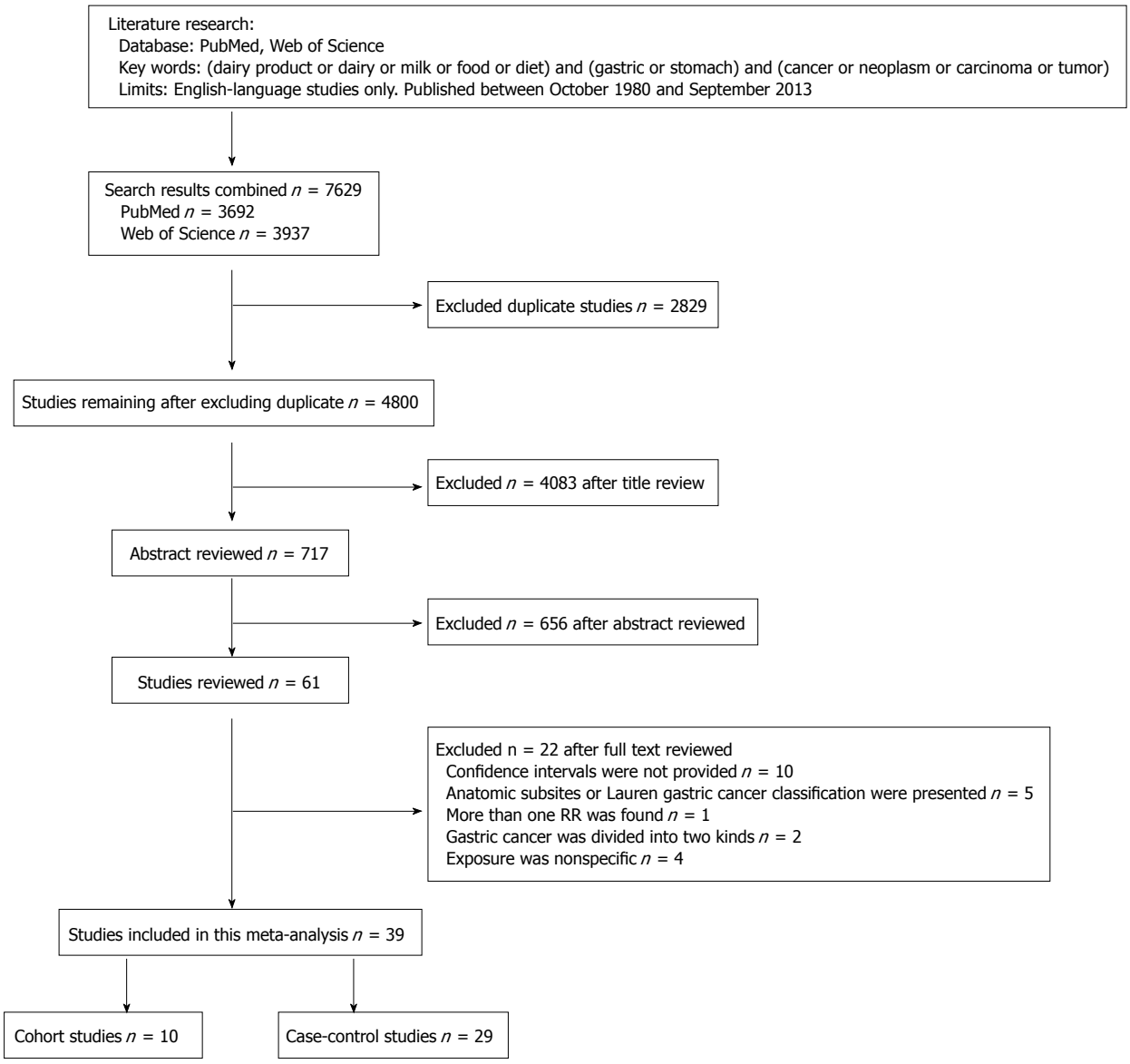

Figure 1 Flow chart of the selection of publications included in this meta-analysis.

fects model or the random effects model to compute the summary relative risks (SRRs) and 95%CIs. The causes of heterogeneity were investigated by subgroup analyses. We conducted a sensitivity analysis by omitting one study in turn and examining whether the results were influenced by any single study. Funnel plots, the Begg's adjusted rank correlation test[47], and the Egger's regression asymmetry test[48] were used to assess the publication bias ($P < 0.10$ was taken to indicate significant publication bias). We performed all analyses with STATA11.0 software (STATA, College Station, TX, United States). All statistical tests were two-sided.

RESULTS

Study characteristics and quality assessment

We found 39 studies[4,24,39,49-84] that were potentially eligible for inclusion in this meta-analysis, including 10 cohort studies[49-58] and 29 case-control studies[4,24,39,59-84]. The process of selecting studies is shown in Figure 1. Of the 10 cohort studies, 3 were carried out in the United States, 4 in Japan, 2 in Europe, and 1 in South Korea (Table 1). Of the 29 case-control studies, 5 were carried out in Japan; 4 in the United States; 3 in China; 2 each in Iran, Poland, Turkey, and Italy; and 1 each in Germany, Sweden, Portugal, France, Mexico, Venezuela, South Korea, Serbia, and Uruguay. One case-control study[39] had two control groups (population- and hospital-based) (Table 2).

The quality scores of the included studied are presented in Tables 3 and 4. The quality scores ranged from 5 to 8 for the case-control studies and 7 to 9 for the cohort studies.

Dairy products

Highest *vs* lowest intake categories: Thirty-eight studies[4,24,39,49-83] presented results on the comparison between the highest *vs* lowest dairy consumption categories and gastric cancer risk. We eliminated one study[83] because

Table 1 Characteristics of published cohort studies on dairy product consumption and gastric cancer risk

Ref.	Region and design	No. of cases (outcome)	Sample size	Follow-up (yr)	Type of meat and consumption categories	Adjusted RR (95%CI)	Covariate adjustments
Nomura *et al*[49], 1990	United States; cohort	150 (incidence)	7990 men	19	Milk (times/wk)		Age
					≤ 1	1.0	
					2-4	1.5 (0.8-2.5)	
					≥ 5	1.2 (0.8-1.6)	
					Ice cream (times/wk)		
					≤ 1	1.0	
					2-4	0.9 (0.6-1.3)	
					≥ 5	1.1 (0.7-1.8)	
					Butter, margarine, cheese (times/wk)		
					≤ 1	1.0	
					2-4	1.1 (0.5-2.1)	
					≥ 5	1.4 (0.9-2.2)	
Kneller *et al*[50], 1991	United States; cohort	75 (mortality)	17633 men	20	Dairy		Year of birth and current cigarette smoking
					Quartiles	1.00	
						1.2 (0.67-2.26)	
						1.1 (0.61-2.10)	
						1.2 (0.61-2.44)	
					Milk (glasses/d)		
					< 1	1.00	
					1	1.4 (0.76-2.74)	
					2-3	0.9 (0.45-1.70)	
					≥ 4	2.4 (1.10-5.04)	
					Used before but not currently	1.2 (0.50-2.68)	
Galanis *et al*[51], 1998	United States; cohort	108 (44 women, 64 men) (incidence)	11907 (6297 women, 5610 men)	14.8	Milk (cups/d)	Women	Age, years of education, Japanese place of birth, gender. Among man also adjusted for cigarette smoking and alcohol intake status
					0	1.0	
					≥ 1	1.0 (0.5-1.8)	
					Milk (cups/d)	Men	
					0	1.0	
					≥ 1	1.0 (0.6-1.7)	
					Milk (cups/d)	Total (women and men)	
					0	1.0	
					≥ 1	1.0 (0.7-1.5)	
Ngoan *et al*[52], 2002	Japan; cohort	116 (39 women, 77 men) (mortality)	13250 (7333 women, 5917 men)	10.5	Fresh milk	Women	Women or men: adjust for age
					≤ 2-4 times/mo		Total: adjust for age, sex, smoking, processed meat, liver, cooking or salad oil, suimono and pickled food
					2-4 times/wk	0.9 (0.3-2.3)	
					≥ 1 time/d	1.3 (0.6-2.6)	
					Fresh milk	Men	
					≤ 2-4 times/mo		
					2-4 times/wk	1.3 (0.7-2.4)	
					≥ 1 time/d	0.9 (0.5-1.6)	
					Fresh milk	Total (women and men)	
					≤ 2-4 times/mo		
					2-4 times/wk	1.5 (0.8-3.0)	
					≥ 1 time/d	0.8 (0.4-1.6)	
					Milk products	Women	
					≤ 2-4 times/mo		
					2-4 times/wk	1.2 (0.3-5.6)	
					≥ 1 time/d	3.1 (0.8-11.6)	
					Milk products	Man	
					≤ 2-4 times/mo		
					2-4 times/wk	1.7 (0.8-3.6)	
					≥ 1 time/d	1.5 (0.5-4.2)	
					Milk products	Total (women and men)	
					≤ 2-4 times/mo		
					2-4 times/wk	1.3 (0.6-2.8)	
					≥ 1 time/d	1.4 (0.5-3.6)	
					Margarine	Women	
					≤ 2-4 times/mo		
					2-4 times/wk	0.6 (0.2-1.9)	
					≥ 1 time/d	0.9 (0.3-2.9)	
					Margarine	Man	
					≤ 2-4 times/mo		
					2-4 times/wk	1.1 (0.5-2.1)	
					≥ 1 time/d	1.1 (0.5-2.6)	

					Margarine	Total (women and men)	
					≤ 2-4 times/mo		
					2-4 times/wk	0.8 (0.4-1.8)	
					≥ 1 time/d	0.7 (0.3-1.8)	
Khan *et al*[53], 2004	Japan; cohort	51 (15 women and 36 men) (mortality)	3158 (1634 women, 1524 men)	14.8	Milk	Women	Women: adjust for age, health status, health education, health screening and smoking
					A		
					B	1.0 (0.4-3.0)	
					Milk	Men	
					A		
					B	1.1 (0.5-2.2)	Men: adjust for age, smoking
					Butter/margarine	Women	
					A		
					B	0.6 (0.2-2.3)	
					Butter/margarine	Men	
					A		
					B	1.7 (0.9-3.2)	
					Cheese	Women	
					A		
					B	1.2 (0.3-5.4)	
					Cheese	Men	
					A		
					B	1.2 (0.5-3.0)	
Tokui *et al*[54], 2005	Japan; cohort	859 (285 women, 574 men) (mortality)	110792 women and men	11	Milk	Women	Age
					None	1.00 (Referent)	
					1-2/mo	0.62 (0.33-1.18)	
					1-2/wk	0.90 (0.58-1.38)	
					3-4/wk	0.78 (0.50-1.21)	
					≥ 1/d	0.83 (0.60-1.13)	
					Milk	Men	
					None	1.00 (Referent)	
					1-2/mo	1.13 (0.79-1.63)	
					1-2/wk	1.17 (0.87-1.58)	
					3-4/wk	1.08 (0.79-1.48)	
					≥ 1/d	1.06 (0.84-1.35)	
					Yogurt	Women	
					None	1.00 (Referent)	
					1-2/mo	0.95 (0.63-1.43)	
					1-2/wk	1.38 (0.93-2.05)	
					3-4/wk	0.85 (0.44-1.63)	
					≥ 1/d	0.88 (0.47-1.64)	
					Yogurt	Men	
					None	1.00 (Referent)	
					1-2/mo	0.69 (0.49-0.98)	
					1-2/wk	0.86 (0.58-1.28)	
					3-4/wk	1.22(0.76-1.97)	
					≥ 1/d	0.82 (0.50-1.37)	
					Cheese	Women	
					None	1.00 (Referent)	
					1-2 times/mo	1.31(0.92-1.85)	
					1-2 times/wk	0.93 (0.57-1.52)	
					3-4 times/wk	0.60 (0.24-1.46)	
					≥ 1 times/d	1.18 (0.52-2.69)	
					Cheese	Men	
					None	1.00 (Referent)	
					1-2/mo	0.93 (0.72-1.20)	
					1-2/wk	1.08 (0.80-1.48)	
					3-4/wk	1.32 (0.86-2.04)	
					≥ 1/d	0.79 (0.39-1.61)	
					Butter	Women	
					None	1.00 (Referent)	
					1-2/mo	0.76 (0.50-1.17)	
					1-2/wk	1.27 (0.85-1.90)	
					3-4/wk	0.37 (0.14-1.01)	
					≥ 1/d	1.22 (0.65-2.26)	
					Butter	Men	
					None	1.00 (Referent)	
					1-2/mo	0.97 (0.75-1.27)	
					1-2/wk	0.96 (0.70-1.33)	
					3-4/wk	0.92 (0.57-1.47)	
					≥ 1/d	0.70 (0.38-1.29)	

					Margarine	Women	
					None	1.00 (Referent)	
					1-2/mo	0.98 (0.64-1.50)	
					1-2/wk	1.09 (0.74-1.59)	
					3-4/wk	0.69 (0.39-1.22)	
					⩾ 1/d	0.82 (0.50-1.33)	
					Margarine	Men	
					None	1.00 (Referent)	
					1-2/mo	0.83 (0.61-1.12)	
					1-2/wk	1.14 (0.87-1.49)	
					3-4/wk	0.92 (0.62-1.36)	
					⩾ 1/d	0.72 (0.48-1.10)	
Van der Pols *et al*[55], 2007	United Kingdom, Scotland; cohort	770 (mortality)	4383 children	65	Total dairy		Age, sex, energy, fruit, and calcium intakes
					Group 1 (low)	1.00	
					Group 2	1.17 (0.39-3.47)	
					Group 3	1.46 (0.44-4.89)	
					Group 4 (high)	0.81 (0.09-7.34)	
					Milk (cups/d)		
					< 0.5	1.00	
					0.5-0.8	1.17 (0.41-3.34)	
					> 0.8 - < 1.2	1.40(0.46-4.26)	
					⩾ 1.2	0.79 (0.11-5.73)	
Pham *et al*[56], 2010	Japan; cohort	477 (157 women, 320 men) (mortality)	63403 (women 37 673, men 25 730)	-	Dairy products pattern (factor score)	Women	Age, tobacco smoking status, history of gastric ulcer, stomach cancer screening, body mass index, educational level, and total energy intake
					Quartiles	1.00	
						0.96 (0.64-1.45)	
						0.74 (0.47-1.18)	
						0.77 (0.48-1.23)	
					Dairy products pattern (factor score)	Men	
					Quartiles	1.00	
						0.82 (0.61-1.10)	
						0.74 (0.54-1.01)	
						0.72 (0.52-0.99)	
Buckland *et al*[57], 2010	European countries; cohort	449 (190 women, men 259) (incidence)	485044 (women 340467, men 144577)	8.9	Dairy products	Women	Sex, body mass index, educational level, smoking status, cigarette smoking intensity, and total energy intake.
					Tertiles	1 (reference)	
						1.22 (0.84-1.77)	
						0.97 (0.65-1.45)	
					Dairy products	Men	
					Tertiles	1 (reference)	
						0.86 (0.63-1.17)	
						0.98 (0.70-1.37)	
					Dairy products	Total (women and men)	
					Tertiles	1 (reference)	
						1.01 (0.80-1.27)	
						0.97 (0.75-1.25)	
Ko *et al*[58], 2013	South Korea; cohort	166 (incidence)	9724 women and men	8.5	Dairy products	Total (women and men)	Total: adjust for age, sex, cigarette smoking, body mass index, alcohol drinking, and area of residence Women or men: adjust for age, cigarette smoking, body mass index, alcohol drinking, and area of residence
					Almost never		
					1-4 times/mo	1.15 (0.78-1.70)	
					1-4 times/wk	1.25 (0.82-1.92)	
					⩾ 1 time/d	1.30 (0.83-2.06)	
					Dairy products	Women	
					Low intake		
					High intake	1.10 (0.91-1.33)	
					Dairy products	Men	
					Low intake		
					High intake	1.05 (0.92-1.19)	

A: Reference group = took never + took several times per year + took several times per month; B: Comparison group = took several times per week + took every day. RR: Relative risk (rate ratio or hazard ratio); CI: Confidence interval.

dairy product consumption was analyzed as a continuous variable. The SRR for gastric cancer, comparing the highest and lowest dairy product consumption categories, was 1.06 (95%CI: 0.95-1.18). Significant heterogeneity was seen among these studies (Q = 112.61; P = 0.000; I^2 =67.1%). Both Egger's test (P = 0.135) and Begg's test (P = 0.365) had symmetric funnel plots and lacked any indication of publication bias (Figure 2).

Sensitivity analysis: We conducted a sensitivity analysis by omitting one study at a time and observing its influence on the overall estimate. The SRR for dairy product consumption and gastric cancer risk was 1.06 (95%CI: 0.94-1.18) after excluding a study by Khan *et al*[53], which

Table 2 Characteristics of published case-control studies on dairy product consumption and gastric cancer risk

Ref.	Region and design	Cases/ controls	Type of item and consumption categories	Adjusted RR (95%CI)	Covariate adjustments
Correa *et al*[59], 1985	United States; case control (hospital based)	391/391	Dairy products	Whites 1.06 (0.68-1.63)	Age, sex, respondent status, education, income, tobacco, and alcohol use
			Dairy products	Blacks 0.85 (0.53-1.34)	
Wu-Williams *et al*[60], 1990	United States; case control (population based)	137/137	Milk		
			≤ 1/wk	1.0	
			≥ 2-4/wk	0.8 (0.4-1.7)	
			≥ 5/wk	1.0 (0.6-1.7)	
Mettlin *et al*[24], 1990	United States; case control (hospital based)	115/1300	Whole Milk		Age, sex, smoking history, education, and country of residence
			None	1.0	
			< Daily	2.9 (1.7-4.9)	
			Daily	3.9 (2.3-6.6)	
			2%Milk		
			None	1.0	
			< Daily	0.5 (0.3-0.9)	
			Daily	0.4 (0.2-0.6)	
			Skim Milk		
			None	1.0	
			< Daily	1.0 (0.5-2.3)	
			Daily	0.5 (0.2-1.3)	
Boeing *et al*[61], 1991	Germany; case control (hospital based)	143/579	Milk		Milk and dairy products: adjust for age, sex, hospital
			Tertiles	1.0	
				1.23 (0.77-1.97)	Cheese: adjust for age, sex, hospital, raw vegetables, citrus fruit, processed meat, whole-meal bread
				1.31 (0.82-2.10)	
			Dairy products		
			Tertiles	1.0	
				0.71 (0.45-1.12)	
				0.63 (0.39-1.03)	
			Cheese		
			Tertiles	1.0	
				1.09 (0.67-1.75)	
				0.55 (0.30-0.98)	
Boeing *et al*[62], 1991	Poland; case control (hospital based)	741/741	Cheese score		Age, sex, education, occupation, residence
			Low	1.0	
			Moderate	0.92 (0.73-1.17)	
			High	0.92 (0.67-1.26)	
Yu *et al*[63], 1991	China, case control (population based)	84/2676	Milk		Age, sex, family income, family history of stomach cancer, family history of other cancer, history of tuberculosis, blood type, cigarette smoking, alcohol, strong tea, fruit, and milk consumption
			Nonusers	1.0	
			Users	0.9 (0.5-1.7)	
Hoshiyama *et al*[39], 1992	Japan; case control population based hospital based	294/294	Dairy products		Age, sex, administrative division, and smoking status
			≤ 1/wk	1.0	
			2-4/wk	0.6 (0.4-1.0)	Age, sex, area, smoking status
			≥ 5/wk	0.8 (0.6-1.2)	
		294/202	Dairy products		
			≤ 1/wk	1.0	
			2-4/wk	0.9 (0.5-1.6)	
			≥ 5/wk	1.0 (0.7-1.6)	
Memik *et al*[64], 1992	Turkey; case control (population based)	252/609	Milk		
			0-200 mL/wk	1.0	
			200-600 mL/wk	0.91 (0.43-1.94)	
			600 mL/wk	5.33 (3.09-9.26)	
Hansson *et al*[65], 1993	Sweden; case control (population based)	338/669	Whole milk (mL/wk)		Age, gender, SES
			≤ 199		
			> 199-2700	1.19 (0.68-2.05)	
			> 2700-4100	1.58 (0.97-2.59)	
			> 4100-6900	1.35 (0.83-2.20)	
			> 6900	1.73 (1.02-2.94)	
			Skimmed milk (mL/wk)		
			0		
			> 0	0.77 (0.53-1.12)	
			Soured milk (times/mo)		
			≤ 0.9		
			> 0.9-7	0.82 (0.54-1.24)	

			> 7-11	0.84 (0.55-1.26)	
			> 11-19	0.81 (0.51-1.30)	
			> 19	0.90 (0.58-1.42)	
			Cheese (times/mo)		
			⩽ 7		
			> 7-29	1.03 (0.64-1.65)	
			> 29-59	0.84 (0.53-1.31)	
			> 59	0.79 (0.48-1.32)	
Inoue *et al*[66], 1994	Japan; case control (hospital based)	668/668	Milk		Sex
			< 3-4 times/wk		
			⩾ 3-4 times/wk	1.0 (0.80-1.25)	
Falcao *et al*[67], 1994	Portugal; case control (hospital based)	74/193	Milk		
			⩽ 0.51/d	0.33 (0.11-0.99)	
Cornée *et al*[68], 1995	France; case control (hospital based)	92/128	Total dairy products		Age, sex, occupation and total energy intake
			Tertiles	1.0	
				1.10 (0.53-2.30)	
				1.80 (0.89-3.66)	
			Milk (all types)		
			Tertiles	1.0	
				1.53 (0.73-3.19)	
				1.57(0.75-3.29)	
			Hard cheese		
			Tertiles	1.0	
				1.09 (0.52-2.26)	
				1.48 (0.74-2.96)	
			Soft cheese		
			Tertiles	1.0	
				0.64 (0.31-1.30)	
				0.92 (0.47-1.80)	
			Yoghurt		
			Tertiles	1.0	
				0.86 (0.40-1.88)	
				0.75 (0.37-1.54)	
			Butter and cream		
			Tertiles	1.0	
				1.31 (0.64-2.71)	
				1.44 (0.71-2.93)	
Muñoz *et al*[4], 1997	Italy; case-control (hospital based)	88/103	Butter (score)		Age, sex, area of residence, and education
			Low	1.0	
			Intermediate/high	1.88 (1.03-3.44)	
			Margarine (score)		
			Low	1.0	
			Intermediate/high	2.42 (1.06-5.51)	
Watabe *et al*[69], 1998	Japan; case control (population based)	242/484	Milk		
			Daily	0.6 (0.43-0.83)	
			Cheese		
			⩾ 3/wk	0.83 (0.51-1.33)	
			Butter		
			⩾ 3/wk	1.57 (0.96-2.53)	
			Yogurt		
			Daily	0.66 (0.38-1.09)	
Ward *et al*[70], 1999	Mexico; case control (population based)	220/752	Dairy products (times/wk)		Age, gender, total calories, chili pepper consumption, added salt, history of peptic ulcer, cigarette smoking, SES
			< 5	1.0	
			5-10	2.1 (1.2-3.7)	
			11-16	2.3 (1.2-4.2)	
			⩾ 17	2.7 (1.4-5.0)	
Muñoz *et al*[71], 2001	Venezuela, case control (population based)	292/485	Dairy products		Age, sex, tobacco, alcohol, total calories and SES
			Quartiles	1.0	
				1.58 (0.98-2.55)	
				2.08 (1.30-3.32)	
				2.43 (1.46-4.04)	
Kim *et al*[72], 2002	Korea; case control (hospital based)	136/136	Milk and milk products		Age, sex, SES, family history and refrigerator use
			Low	1.00	
			Medium	0.75 (0.42-1.35)	
			High	0.68 (0.34-1.36)	
Chen *et al*[73], 2002	United States; case control (population based)	124/449	Dairy products (times/wk)		Age, sex, energy, respondent type, body mass index, alcohol use, tobacco use, education, family history, vitamin supplement
			Quartiles	0.79 (0.35-1.7)	
				1.40 (0.68-2.8)	
				0.76 (0.34-1.7)	

			Milk (times/wk)		
			Quartiles	0.72 (0.33-1.6)	
				1.7 (0.85-3.5)	
				0.86 (0.39-1.9)	
Ito *et al*[74], 2002	Japan; case control (hospital based)	508/36490	Milk		Age, year, season of fist hospital visit, smoking habit, family history of gastric cancer
			Almost never	1.0	
			Occasionally	0.98 (0.75-1.27)	
			3-4 times/wk	1.09 (0.85-1.39)	
			Everyday	0.85 (0.62-1.18)	
Lissowska *et al*[75], 2004	Poland; case control (population based)	274/463	Diary product (times/wk)		Age, sex, education, smoking, and calories from food
			< 18.9	1.0	
			18.9-25.8	0.96 (0.63-1.46)	
			25.9-32.9	0.87 (0.54-1.40)	
			> 32.9	0.94 (0.57-1.54)	
De Stefani *et al*[76], 2004	Uruguay; case control (hospital based)	240/960	Dairy foods	Total (women and men)	Total: adjust for age, sex, residence, urban/rural status, education, body mass index, and total energy intake
			Tertiles	1.0	
				1.24 (0.85-1.80)	
				0.89 (0.59-1.33)	
			Dairy foods	Women	Women or men: adjust for age, residence, urban/rural status, education, body mass index, tobacco smoking, alcohol drinking, and total energy intake
			Highest tertile *vs* Lowest tertile	1.45 (0.64-3.29)	
			Dairy foods	Men	
			Highest tertile *vs* Lowest tertile	0.75 (0.46-1.20)	
Huang *et al*[77], 2004	Japan; case control (hospital based)	GCFH(+) 464/6 310	Milk		Age, sex
			< 1/d		
		GCFH(-) 1524/44 396	⩾ 1/d	0.86 (0.70-1.05)	
			Milk		
			< 1/d		
			⩾ 1/d	0.98 (0.88-1.09)	
Fei *et al*[78], 2006	China; case control (hospital based)	189/567	Milk products		
			High *vs* low	0.690 (0.524-0.907)	
Lucenteforte *et al*[79], 2008	Italy; case control (hospital based)	230/547	Milk and yogurt (servings/wk)		Age, sex, education, year of interview, body mass index, tobacco smoking, family history of stomach cancer, and total energy intake
			⩽ 0.5	1.0	
			> 0.5-4.5	0.77 (0.45-1.33)	
			> 4.5-7	0.81 (0.50-1.30)	
			> 7-9	0.88 (0.50-1.54)	
			> 9-24	1.06 (0.64-1.78)	
			Cheese (servings/wk)		
			⩽ 1.8	1.0	
			> 1.8-3.0	1.38 (0.79-2.41)	
			> 3.0-3.8	1.43 (0.82-2.49)	
			> 3.8-5.1	1.22 (0.70-2.15)	
			> 5.1-10.7	1.63 (0.92-2.90)	
Chen *et al*[80], 2009	China; case control (hospital based)	41/205	Dairy products (times/wk)		Age and years of schooling
			< 3	1.00	
			⩾ 3	0.72 (0.13-4.15)	
			Milk (/d)		
			No	1.00	
			Yes	1.02 (0.16-7.08)	
Pourfarzi *et al*[81], 2009	Iran; case control (population based)	217/394	Dairy products		Age, sex, education, family history of gastric cancer, citrus fruits, garlic, onion, red meat, fish, dairy products, strength and warmth of tea, preference for salt intake and *H. pylori*
			⩽ 2 times/wk	1.00	
			3-4/wk	3.77 (1.92-7.42)	
			> 1/d	2.28 (1.23-4.22)	
			Cheese		
			⩽ 2 times/wk	1.00	
			3-4/wk	1.00 (0.39-2.56)	
			> 1/d	1.16 (0.54-2.51)	
Lazarevic *et al*[82], 2010	Serbia; case control (hospital based)	102/204	Milk		Age, sex, residence, education, meals regularity, tobacco smoking, and history of cancer in the first degree relatives
			Tertiles	1.00	
				2.60 (0.86-7.87)	
				5.08 (1.59-10.16)	
			Dairy		
			Tertiles	1.00	
				0.42 (0.20-1.23)	
				0.63 (0.33-1.72)	
Icli *et al*[83], 2011	Turkey; case control (hospital based)	253/253	Milk		
			Low	1.0	
			Moderate	1.4 (0.7-2.6)	
			High		

			Yogurt		
			Low	1.0	
			Moderate	0.8 (0.4-1.5)	
			High	1.0 (0.2-4.9)	
Pakseresht *et al*[84], 2011	Iran; case control (population based)	286/304	Dairy		Age, sex, education, living area, smoking, gastric symptoms, income, owning refrigerator, duration of using refrigerator, seeds preparing method, frying *H. pylori* infection.
			Per 100 g	1.01 (0.90-1.13)	

RR: Relative risk (rate ratio or hazard ratio); CI: Confidence interval; SES: Socio-economic status; PCC: Population-based case-control; HCC: Hospital-based case-control; *H. pylori*: *Helicobacter pylori*.

Table 3 Methodological quality of cohort studies included in this meta-analysis

Ref.	Representativeness of the exposed cohort	Selection of the non exposed cohort	Ascertainment of exposure	Outcome of interest not present at start of study	Control for important factors[1]	Assessment of outcome	Follow-up long enough for outcomes to occur[2]	Adequacy of follow-up of cohorts[3]	Total quality scores
Nomura *et al*[49], 1990	*	*	*	*	*	*	*	*	8
Kneller *et al*[50], 1991	*	*	*	*	*	*	*	*	8
Galanis *et al*[51], 1998	*	*	*	*	**	*	*	*	9
Ngoan *et al*[52], 2002	*	*	*	*	**	*	*	*	9
Khan *et al*[53], 2004	*	*	*	*	**	*	*	*	9
Tokui *et al*[54], 2005	*	*	*	*	*	*	*	*	8
Van der Pols *et al*[55], 2007	*	*	-	*	*	*	*	*	7
Pham *et al*[56], 2010	*	*	*	*	**	*	-	*	8
Buckland *et al*[57], 2010	*	*	*	*	*	*	*	*	8
Ko *et al*[58], 2013	*	*	*	*	**	*	*	*	9

[1]A maximum of two stars could be awarded for this item. Studies that controlled for age received one start, whereas studies that controlled for smoking or drinking received an additional start; [2]A cohort study with a follow-up time > 8 years was awarded one start; [3]A cohort study with a follow-up rate > 70% was awarded one start.

had 9 stars in the quality assessment. The SRR was 1.06 (95%CI: 0.94-1.19) after excluding another study by Correa *et al*[59] that had divided participants into two ethnic groups. The SRR changed from 1.06 to 1.07 (95%CI: 0.94-1.23) after excluding the study by Huang *et al*[77] in which participants had a family history of gastric cancer.

Subgroup analysis: In a subgroup analysis performed according to the study design, the SRR for dairy product consumption in hospital-based case-control studies[4,24,59,61,62,66-68,72,74,76-80,82,83] was 0.94 (95%CI: 0.83-1.08). The SRR in population-based case-control studies[39,60,63-65,69-71,73,75,81] was 1.36 (95%CI: 0.94-1.96); for cohort studies[49-58], it was 1.00 (95%CI: 0.89-1.14) (Figure 3A). The population-based case-control studies had significant heterogeneity (Q = 59.14; P = 0.000; I^2 = 83.1%). The cohort studies and hospital-based case-control studies did not have significant heterogeneity (Q = 12.90; P = 0.167; I^2 = 30.2% and Q = 30.50; P = 0.016; I^2 = 47.5%, respectively).

When we analyzed the subgroups according to the geographic region, there was a modest, nonsignificant effect of dairy product consumption on gastric cancer for studies performed in United States[24,49-51,59,60,70,71,73,76] (SRR = 1.20; 95%CI: 0.95-1.50; Q = 20.18; P = 0.017; I^2 = 55.4%) and Europe[4,55,57,61,62,64,65,67,68,75,79,82,83] (SRR = 1.15; 95%CI: 0.86-1.55; Q = 55.50; P = 0.000; I^2 = 78.4%), but this relationship did not hold for studies in Asia[39,52-54,56,58,63,66,69,72,74,77,78,80,81] (SRR = 0.92; 95%CI: 0.83-1.02; Q = 23.08; P = 0.059; I^2 = 39.3%) (Figure 3B).

In the subgroup analysis according to sex, the SRR was 0.98 (95%CI: 0.90-1.07) in men[51-54,56-58,76] and 1.00 (95%CI: 0.88-1.13) in women[51-54,56-58,76]. These studies lacked heterogeneity (Q = 9.42; P = 0.224; I^2 =25.7% for men and Q = 6.70; P = 0.460; I^2 = 0.0% for women) (Figure 3C).

We also stratified these studies, adjusting for smoking and drinking. The SRR for gastric cancer in 17 studies that were adjusted for smoking[24,39,50,52,53,56-59,63,70,71,73-75,79,82] was 1.06 (95%CI: 0.90-1.25); the SRR in 5 studies that were adjusted for drinking[58,59,63,71,73] was 1.19 (95%CI:

Table 4 Methodological quality of case-control studies included in this meta-analysis

Ref.	Adequate definition of cases	Representativeness of cases	Selection of control	Definition of control	Control for important factor or additional factor[1]	Exposure assessment	Same method of ascertainment for cases and cohorts	Nonresponse rate[2]	Total quality scores
Correa *et al*[59], 1985	*	*	-	*	**	*	*	-	7
Wu-Williams *et al*[60], 1990	*	*	*	-	-	*	*	-	5
Mettlin *et al*[24], 1990	-	*	-	*	**	*	*	-	6
Boeing *et al*[61], 1991	*	*	-	*	*	*	*	-	6
Boeing *et al*[62], 1991	*	*	-	*	*	*	*	-	6
Yu *et al*[63], 1991	*	*	*	*	**	*	*	-	8
Hoshiyama *et al*[39], 1992	*	*	*	-	**	*	*	-	7
Memik *et al*[64], 1992	*	*	*	*	-	-	*	-	5
Hansson *et al*[65], 1993	*	*	*	-	*	*	*	-	6
Inoue *et al*[66], 1994	*	*	-	*	-	*	*	*	6
Falcao *et al*[67], 1994	*	*	-	*	-	*	*	-	5
Cornée *et al*[68], 1995	*	*	-	*	*	*	*	-	6
Muñoz *et al*[4], 1997	*	*	-	*	*	*	*	-	6
Watabe *et al*[69], 1998	*	*	*	-	-	*	*	-	5
Ward *et al*[70], 1999	*	*	*	*	**	*	*	-	8
Muñoz *et al*[71], 2001	*	*	*	-	**	*	*	-	7
Kim *et al*[72], 2002	*	*	-	*	*	*	*	-	6
Chen *et al*[73], 2002	*	*	*	-	**	*	*	-	7
Ito *et al*[74], 2002	*	*	-	*	**	*	*	-	7
Lissowska *et al*[75], 200	*	*	*	-	**	*	*	-	7
De Stefani *et al*[76], 2004	*	*	-	*	**	*	*	-	7
Huang *et al*[77], 2004	-	*	-	*	*	*	*	-	5
Fei *et al*[78], 2006	*	*	-	*	-	*	*	-	5
Lucenteforte *et al*[79], 2008	*	*	-	*	**	*	*	-	7
Chen *et al*[80], 2009	*	*	-	*	*	*	*	-	6
Pourfarzi *et al*[81], 2009	*	*	*	*	*	*	*	-	7
Lazarevic *et al*[82], 2010	*	*	-	*	**	*	*	-	7
Icli *et al*[83], 2011	*	*	-	*	-	*	*	-	5
Paksereshat *et al*[84], 2011	*	*	*	*	**	*	*	-	8

[1]A maximum of two stars could be awarded for this item. Studies that controlled for age received one start, whereas studies that controlled for smoking or drinking received an additional start; [2]One star was assigned if there was no significant difference in the response rate between case and control subjects by using the χ^2 test (P = NS). NS: Not significant.

0.81-1.74). There was significant heterogeneity between these smoking-adjusted studies (Q = 35.00; P = 0.004; I^2 = 54.3%) and drinking-adjusted studies (Q = 11.47; P = 0.022; I^2 = 65.1%) (Table 5).

Individual dairy product items

Seven cohort studies[49-55], 6 population-based case-control studies[60,63-65,69,73], and 10 hospital-based case-control studies[24,61,66-68,74,77,80,82,83] of milk consumption were in-

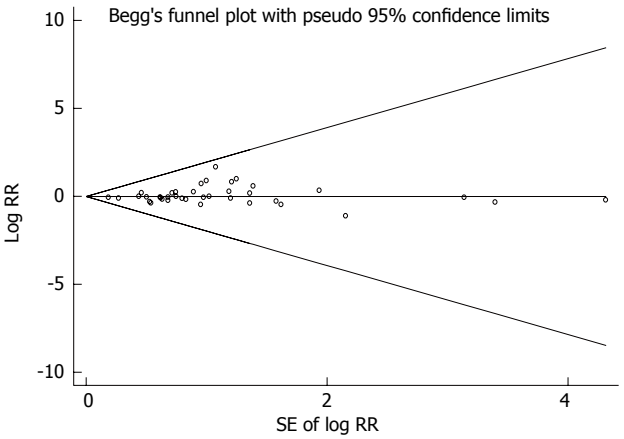

Figure 2 Funnel plot of studies evaluating the association between dairy product consumption and gastric cancer risk.

cluded in our meta-analysis. When we analyzed the effects of the study design, the SRR was 1.05 (95%CI: 0.89-1.23) in cohort studies, 1.16 (95%CI: 0.62-2.17) in population-based case-control studies, and 1.09 (95%CI: 0.87-1.35) in hospital-based case-control studies (Figure 4A). There was significant heterogeneity for population-based case-control studies (Q = 45.23; P = 0.000; I^2 = 88.9%) and hospital-based case-control studies (Q = 21.23; P = 0.012; I^2 = 57.6%) but not for cohort studies (Q = 6.48; P = 0.372; I^2 = 7.4%). We analyzed the geographic region, including studies performed in America[24,49-51,60,73] (SRR = 1.13; 95%CI: 0.92-1.39; Q = 4.99; P = 0.417; I^2 = 0.0%), Europe[55,61,64,65,67,68,82,83] (SRR = 1.58; 95%CI: 0.89-2.80; Q = 37.37; P = 0.000; I^2 = 81.3%), and Asia[52-54,63,66,69,74,77,80] (SRR = 0.93; 95%CI: 0.86-1.00; Q = 8.30; P = 0.404; I^2 = 3.7%). For subgroup analysis according to sex, the SRR of gastric cancer associated with milk consumption was 1.03 (95%CI: 0.85-1.26) in men[51-54] and 0.91 (95%CI: 0.71-1.18) in women[51-54]. These studies lacked heterogeneity (Q = 0.30; P = 0.959; I^2 = 0.0% for men and Q = 1.35; P = 0.717; I^2 = 0.0% for women).

Nine studies on cheese consumption were included in our meta-analysis. When we examined these 9 studies together, the SRR for gastric cancer was 0.95 (95%CI: 0.80-1.12) for individuals in the highest compared with the lowest category of cheese consumption. These studies did not have significant heterogeneity (Q = 8.80; P = 0.360; I^2 = 9.1%). There was no observed publication bias (Egger's test: P = 0.621; Begg's test: P = 0.754). Additionally, we calculated the SRR for gastric cancer separately for three study designs: hospital-based case-control studies[61,62,68,79] (SRR = 0.98; 95%CI: 0.78-1.22), population-based case-control studies[65,69,81] (SRR = 0.86; 95%CI: 0.63-1.18), and cohort studies[53,54] (SRR = 1.02; 95%CI: 0.66-1.58) (Figure 4B). In the subgroup analysis according to the geographic region, studies in Europe[61,62,65,68,79] had an SRR of 0.95 (95%CI: 0.77-1.16; Q = 7.87; P = 0.097; I^2 = 49.2%), whereas studies in Asia[53,54,69,81] had an SRR of 0.96 (95%CI: 0.71-1.29; Q = 0.92; P = 0.820; I^2 = 0.0%).

We included four studies specifically reporting on yogurt consumption[54,68,69,83] in our meta-analysis. The SRR for gastric cancer for the highest *vs* lowest yogurt consumption category was 0.79 (95%CI: 0.41-1.51) in hospital-based case-control studies[68,83], 0.66 (95%CI: 0.39-1.12) in population-based case-control studies[69], and 0.84 (95%CI: 0.57-1.24) in cohort studies[54]. When all four studies were examined together, the SRR was 0.77 (95%CI: 0.58-1.03). There was no evidence of heterogeneity (Q = 0.62; P = 0.891; I^2 = 0.0%) or publication bias (Egger's test: P = 0.923; Begg's test: P = 1.000) when comparing these 4 studies. In the subgroup analysis by geographic region, the SRR was 0.79 (95%CI: 0.41-1.51; Q = 0.10; P = 0.747; I^2 = 0.0%) for studies in Europe[68,83] and 0.77 (95%CI: 0.56-1.06; Q = 0.52; P = 0.172; I^2 =0.0%) for studies in Asia[54,69].

Only 3 studies[4,54,69] on butter consumption and gastric cancer risk were analyzed in our meta-analysis. An analysis of all 3 studies showed an SRR of 1.35 (95%CI: 0.88-2.08) for high *vs* low butter consumption. Significant heterogeneity was seen among these 3 studies (Q = 4.40; P = 0.111; I^2 = 54.6%), but there was no publication bias (Egger's test: P = 0.349; Begg's test: P = 0.296).

A limited number of studies (3 in total)[4,52,54] on margarine were included in our meta-analysis. The SRR for gastric cancer was 1.04 (95%CI: 0.51-2.12) in the pooled analysis, which was obtained from comparing the highest and lowest margarine consumption categories. There was significant heterogeneity in these 3 studies (Q = 6.83; P = 0.033; I^2 = 70.7%), but there was no publication bias (Egger's test: P = 0.601: Begg's test: P = 1.000).

DISCUSSION

To the best of our knowledge, this is the first meta-analysis to report on an association between dairy product consumption and gastric cancer risk. Twenty-eight case-control studies and 10 cohort studies were combined to expand the sample size and obtain a more creditable result. The SRR for gastric cancer according to the highest *vs* lowest dairy product consumption category was 1.06 (95%CI: 0.95-1.18). Ten publications[26-35] were excluded from this meta-analysis because they did not provide 95%CIs. The exclusion of those studies reduced the study population, which may have affected our result.

Among the 38 included publications, 1[64] reported an extremely positive association between dairy product consumption and gastric cancer incidence (RR = 5.33). When we excluded this study and recalculated the SRR with the remaining studies, we found that the SRR decreased from 1.06 to 1.01. The modest, nonsignificant risk of gastric cancer from dairy product consumption in this meta-analysis may be attributable to this single study.

Significant heterogeneity was seen among the 38 studies. To investigate the reasons for heterogeneity, we conducted subgroup analyses for the study design, geographic region, sex, and whether there were adjustments for confounders (smoking and drinking). However, we did not find a possible source of heterogeneity, despite the subgroup analyses.

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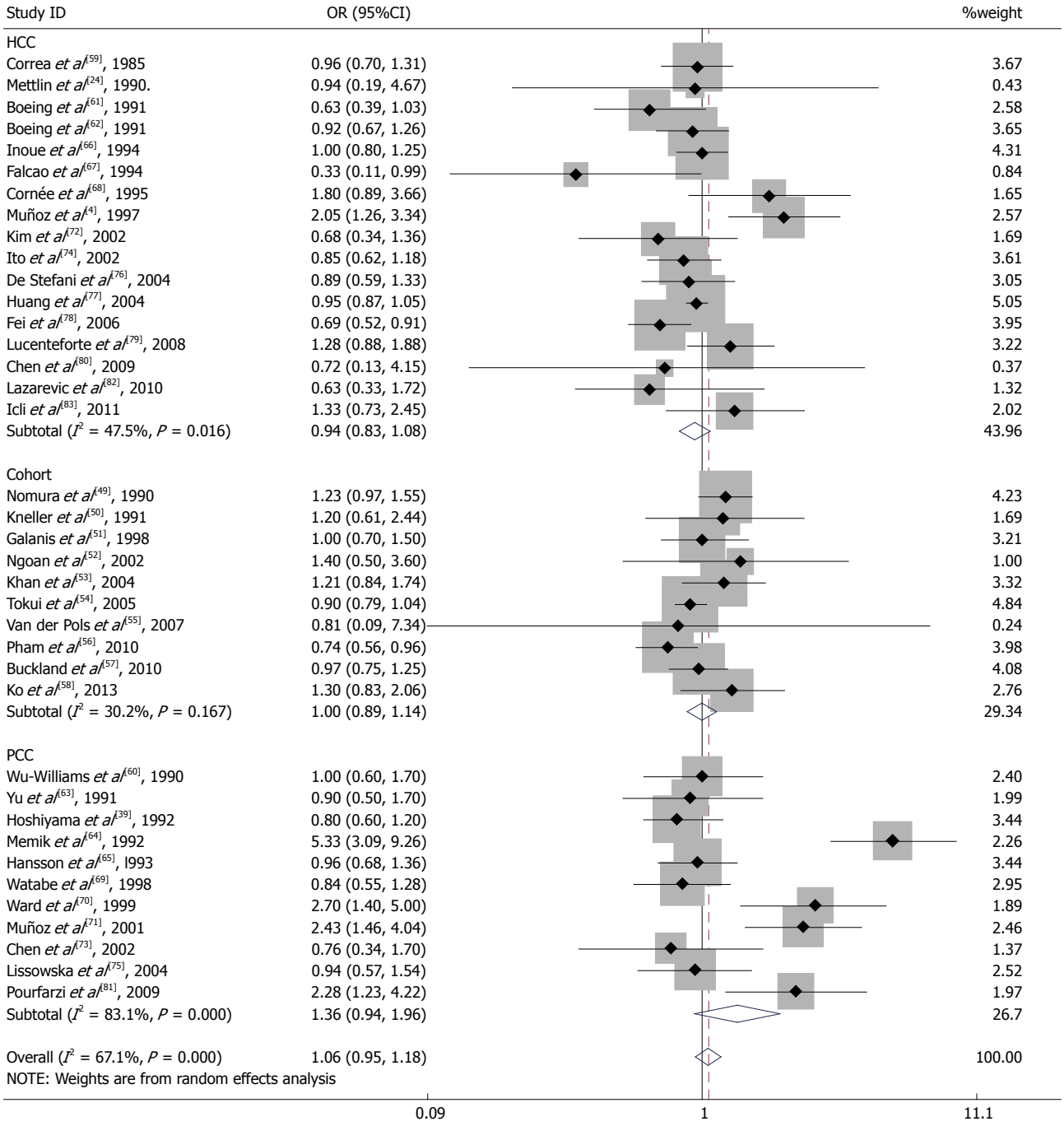
Study ID
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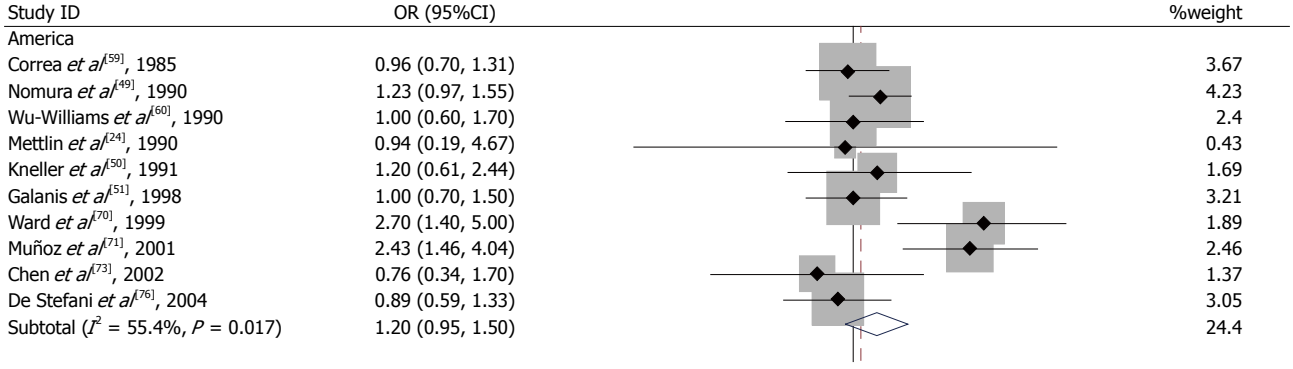
HCC
Correa et al[59], 1985 0.96 (0.70, 1.31) 3.67
Mettlin et al[24], 1990. 0.94 (0.19, 4.67) 0.43
Boeing et al[61], 1991 0.63 (0.39, 1.03) 2.58
Boeing et al[62], 1991 0.92 (0.67, 1.26) 3.65
Inoue et al[66], 1994 1.00 (0.80, 1.25) 4.31
Falcao et al[67], 1994 0.33 (0.11, 0.99) 0.84
Cornée et al[68], 1995 1.80 (0.89, 3.66) 1.65
Muñoz et al[4], 1997 2.05 (1.26, 3.34) 2.57
Kim et al[72], 2002 0.68 (0.34, 1.36) 1.69
Ito et al[74], 2002 0.85 (0.62, 1.18) 3.61
De Stefani et al[76], 2004 0.89 (0.59, 1.33) 3.05
Huang et al[77], 2004 0.95 (0.87, 1.05) 5.05
Fei et al[78], 2006 0.69 (0.52, 0.91) 3.95
Lucenteforte et al[79], 2008 1.28 (0.88, 1.88) 3.22
Chen et al[80], 2009 0.72 (0.13, 4.15) 0.37
Lazarevic et al[82], 2010 0.63 (0.33, 1.72) 1.32
Icli et al[83], 2011 1.33 (0.73, 2.45) 2.02
Subtotal (I^2 = 47.5%, P = 0.016) 0.94 (0.83, 1.08) 43.96
Cohort
Nomura et al[49], 1990 1.23 (0.97, 1.55) 4.23
Kneller et al[50], 1991 1.20 (0.61, 2.44) 1.69
Galanis et al[51], 1998 1.00 (0.70, 1.50) 3.21
Ngoan et al[52], 2002 1.40 (0.50, 3.60) 1.00
Khan et al[53], 2004 1.21 (0.84, 1.74) 3.32
Tokui et al[54], 2005 0.90 (0.79, 1.04) 4.84
Van der Pols et al[55], 2007 0.81 (0.09, 7.34) 0.24
Pham et al[56], 2010 0.74 (0.56, 0.96) 3.98
Buckland et al[57], 2010 0.97 (0.75, 1.25) 4.08
Ko et al[58], 2013 1.30 (0.83, 2.06) 2.76
Subtotal (I^2 = 30.2%, P = 0.167) 1.00 (0.89, 1.14) 29.34
PCC
Wu-Williams et al[60], 1990 1.00 (0.60, 1.70) 2.40
Yu et al[63], 1991 0.90 (0.50, 1.70) 1.99
Hoshiyama et al[39], 1992 0.80 (0.60, 1.20) 3.44
Memik et al[64], 1992 5.33 (3.09, 9.26) 2.26
Hansson et al[65], l993 0.96 (0.68, 1.36) 3.44
Watabe et al[69], 1998 0.84 (0.55, 1.28) 2.95
Ward et al[70], 1999 2.70 (1.40, 5.00) 1.89
Muñoz et al[71], 2001 2.43 (1.46, 4.04) 2.46
Chen et al[73], 2002 0.76 (0.34, 1.70) 1.37
Lissowska et al[75], 2004 0.94 (0.57, 1.54) 2.52
Pourfarzi et al[81], 2009 2.28 (1.23, 4.22) 1.97
Subtotal (I^2 = 83.1%, P = 0.000) 1.36 (0.94, 1.96) 26.7
Overall (I^2 = 67.1%, P = 0.000) 1.06 (0.95, 1.18) 100.00
NOTE: Weights are from random effects analysis
0.09
1
11.1

B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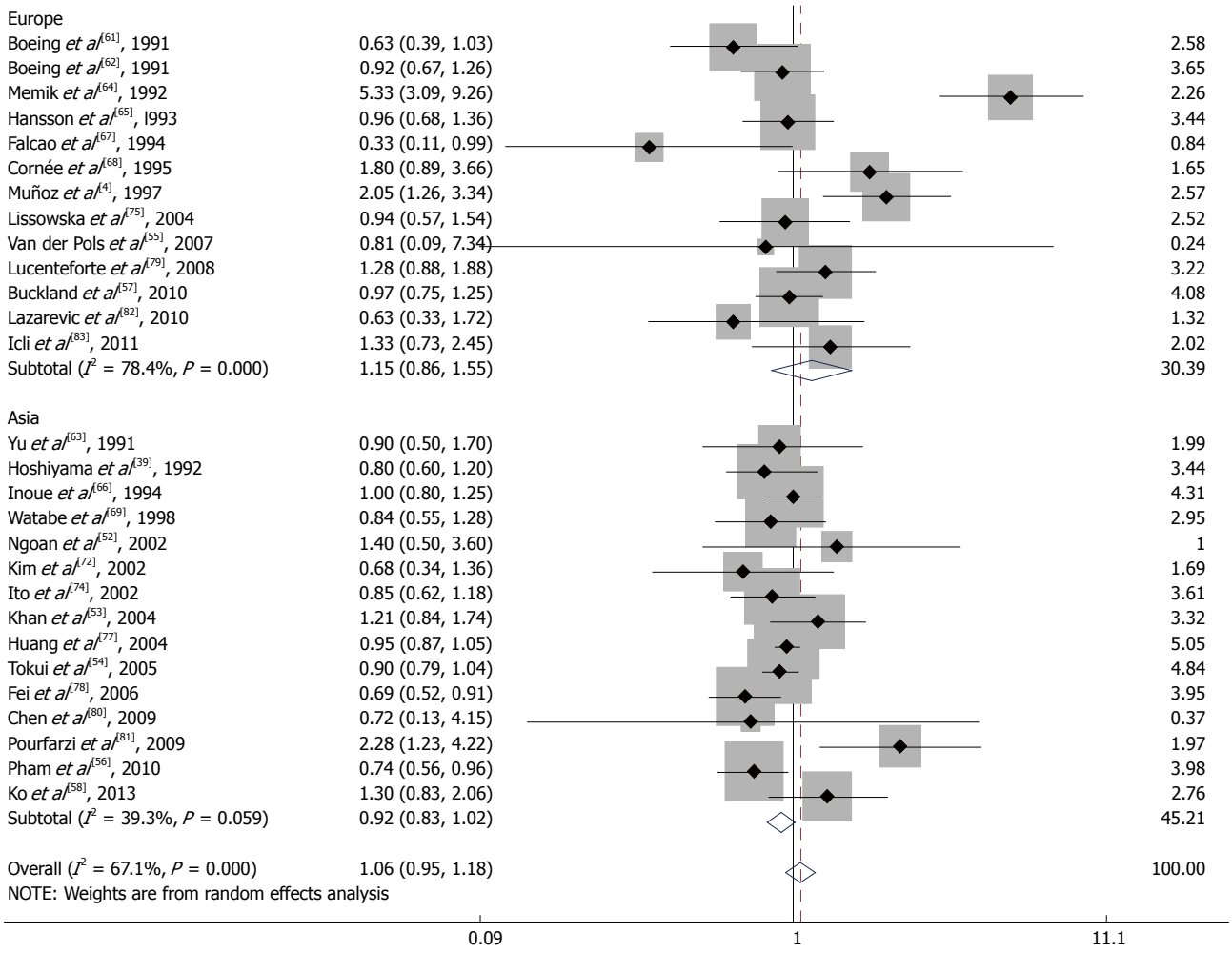
America
Correa et al[59], 1985 0.96 (0.70, 1.31) 3.67
Nomura et al[49], 1990 1.23 (0.97, 1.55) 4.23
Wu-Williams et al[60], 1990 1.00 (0.60, 1.70) 2.4
Mettlin et al[24], 1990 0.94 (0.19, 4.67) 0.43
Kneller et al[50], 1991 1.20 (0.61, 2.44) 1.69
Galanis et al[51], 1998 1.00 (0.70, 1.50) 3.21
Ward et al[70], 1999 2.70 (1.40, 5.00) 1.89
Muñoz et al[71], 2001 2.43 (1.46, 4.04) 2.46
Chen et al[73], 2002 0.76 (0.34, 1.70) 1.37
De Stefani et al[76], 2004 0.89 (0.59, 1.33) 3.05
Subtotal (I^2 = 55.4%, P = 0.017) 1.20 (0.95, 1.50) 24.4



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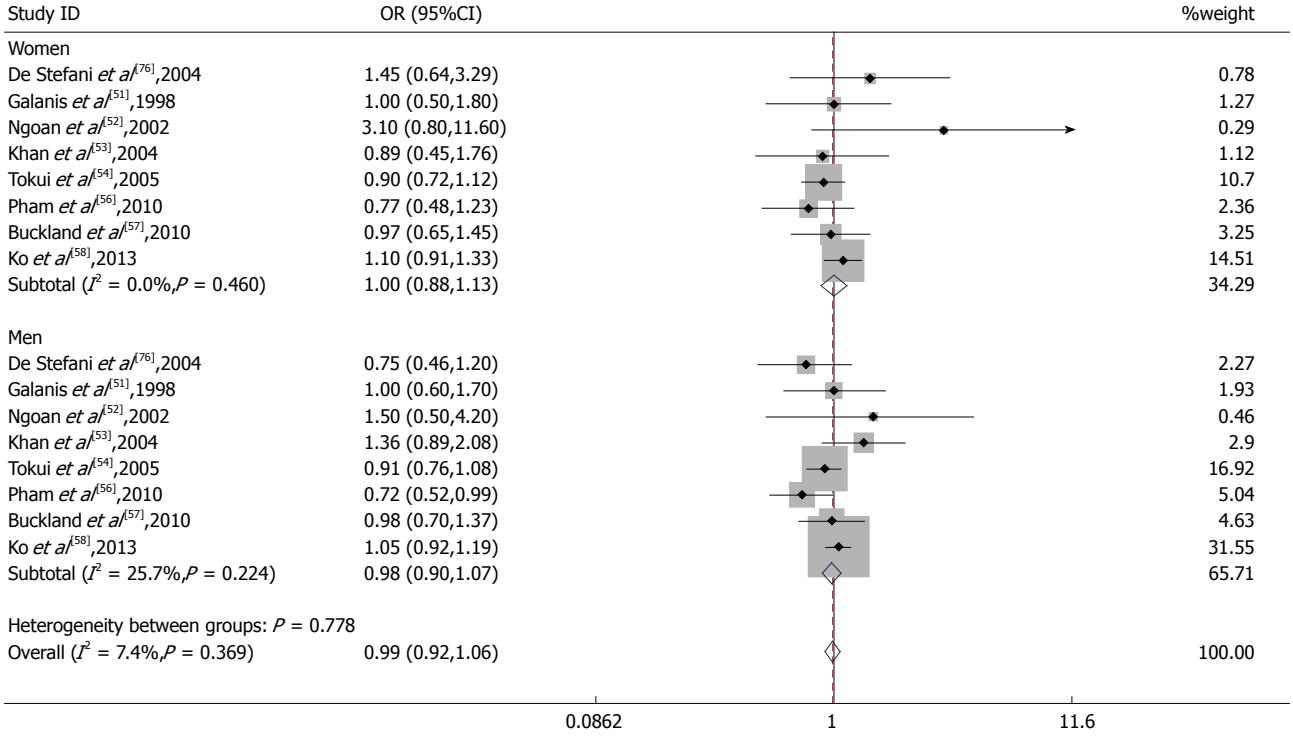

Figure 3 Forest plots of gastric cancer risk associated with dairy product consumption, stratified by study design (A), geographic region (B) and sex (C).

Table 5 Subgroup analysis of relative risks for the association between dairy product consumption and gastric cancer risk

	No. of studies	RR (95%CI)	*Q*-value	pH	I^2
Study design					
All studies	38	1.06 (0.95-1.18)	112.61	0.000	67.1%
Cohort studies	10	1.00 (0.89-1.14)	12.90	0.167	30.2%
HCC studies	17	0.94 (0.83-1.08)	30.50	0.016	47.5%
PCC studies	11	1.36 (0.94-1.96)	59.14	0.000	83.1%
Sex					
Women	8	1.00 (0.88-1.13)	6.70	0.460	0.0%
Men	8	0.98 (0.90-1.07)	9.42	0.224	25.7%
Region					
Asia	15	0.92 (0.83-1.02)	23.08	0.059	39.3%
Europe	13	1.15 (0.86-1.55)	55.50	0.000	78.4%
America	10	1.20 (0.95-1.50)	20.18	0.017	55.4%
Adjustments					
Smoking	17	1.06 (0.90-1.25)	35.00	0.004	54.3%
No smoking	21	1.06 (0.91-1.23)	77.31	0.000	74.1%
Drinking	5	1.19 (0.81-1.74)	11.47	0.022	65.1%
No drinking	33	1.04 (0.93-1.17)	98.41	0.000	67.5%

RR: Relative risk (rate ratio or hazard ratio); CI: Confidence interval.

After performing the subgroup analysis for the study design, discrepancies were observed between case-control studies and the cohort studies. Because exposure information is collected after diagnosing gastric cancer, case-control studies can result in selection bias. Individuals in case-control studies, especially in hospital-based case-control studies, may change their earlier long-term dietary habits to avoid disease-related digestive symptoms. For example, patients with gastric cancer may stop drinking milk because of the onset of symptoms (stomachache, vomiting, and nausea). Patients in hospital-based case-control studies were likely to be health conscious, which could strongly influence their dietary habits and confound the observed association. Moreover, a possible reason for the difference in the risk estimates is that the participants in the prospective cohort and case-control studies had different exposure levels for the highest consumption categories.

We found a nonsignificant, protective effect for dairy product consumption on gastric cancer in Asian populations but did not observe this effect for European and American populations. Ethnic differences, different eating habits, and the gap in economic development may explain this discrepancy. For example, milk is a major animal source of dietary protein in an Asian diet, especially in developing countries; however, milk is essentially a breakfast food in the West. Cheese and yogurt are also popular foods in the West. Approximately 60% of the studies used in our meta-analysis were conducted in Europe and America. Differences in dairy production and aseptic technology may also have affected these results.

Smoking and drinking may increase the risk of gastric cancer. We found a nonsignificant risk of developing gastric cancer from dairy product consumption after adjusting for the two factors independently. In our meta-analysis, nearly 50% of the studies were adjusted for smoking, and < 20% of the studies were adjusted for drinking. Because not enough studies were adjusted for the subjects' smoking and drinking habits, we could not obtain a convincing result.

Different types of individual dairy product produce different effects on the gastric cancer risk. Frequent, long-term dairy product consumption (especially whole milk and butter, which have the highest fat content) can lead to obesity. An animal experiment study[85] has suggested that obesity increases pro-inflammatory immune responses and accelerates *Helicobacter felis*-induced gastric carcinogenesis by enhancing immature myeloid cell trafficking and Th17 response. We found an inverse association between gastric cancer risk and yogurt consumption, but this association was not significant. Yogurt is a type of fermented milk; one study[86] found that *Propionibacterium freudenreichii* (*P. freudenreichii*) - the sole bacterium contained in some fermented milk - could inhibit the adhesion of the causative agent for gastric cancer, *Helicobacter pylori* (*H. pylori*), to digestive epithelial cells and inhibit *H. pylori*-induced damage. The study also reported that the aqueous phase of this fermented milk kills human gastric cancer cells *via* metabolites, including propionate and acetate that are released by the bacterium *P. freudenreichii*. In an animal experiment, *P. freudenreichii*-fermented dairy had an anti-inflammatory effect[87]. Together, these findings imply that *P. freudenreichii*-fermented milk can act as a prophylaxis for gastric cancer. Dairy products, especially milk, contain many essential nutrients, such as conjugated linoleic acid, vitamins, and minerals, which may promote positive health effects[88]. Studies[89] performed in animals and *in vitro* have shown the protective effects of conjugated linoleic acid against carcinogenesis in the forestomach, potentially by inhibiting the cyclooxygenase-2 or lipoxygenase pathway or by inducing the expression of apoptotic genes.

Our meta-analysis has several strengths. First, to the best of our knowledge, this is the first meta-analysis to explore an association between dairy product consumption and gastric cancer risk. We included 10 prospective

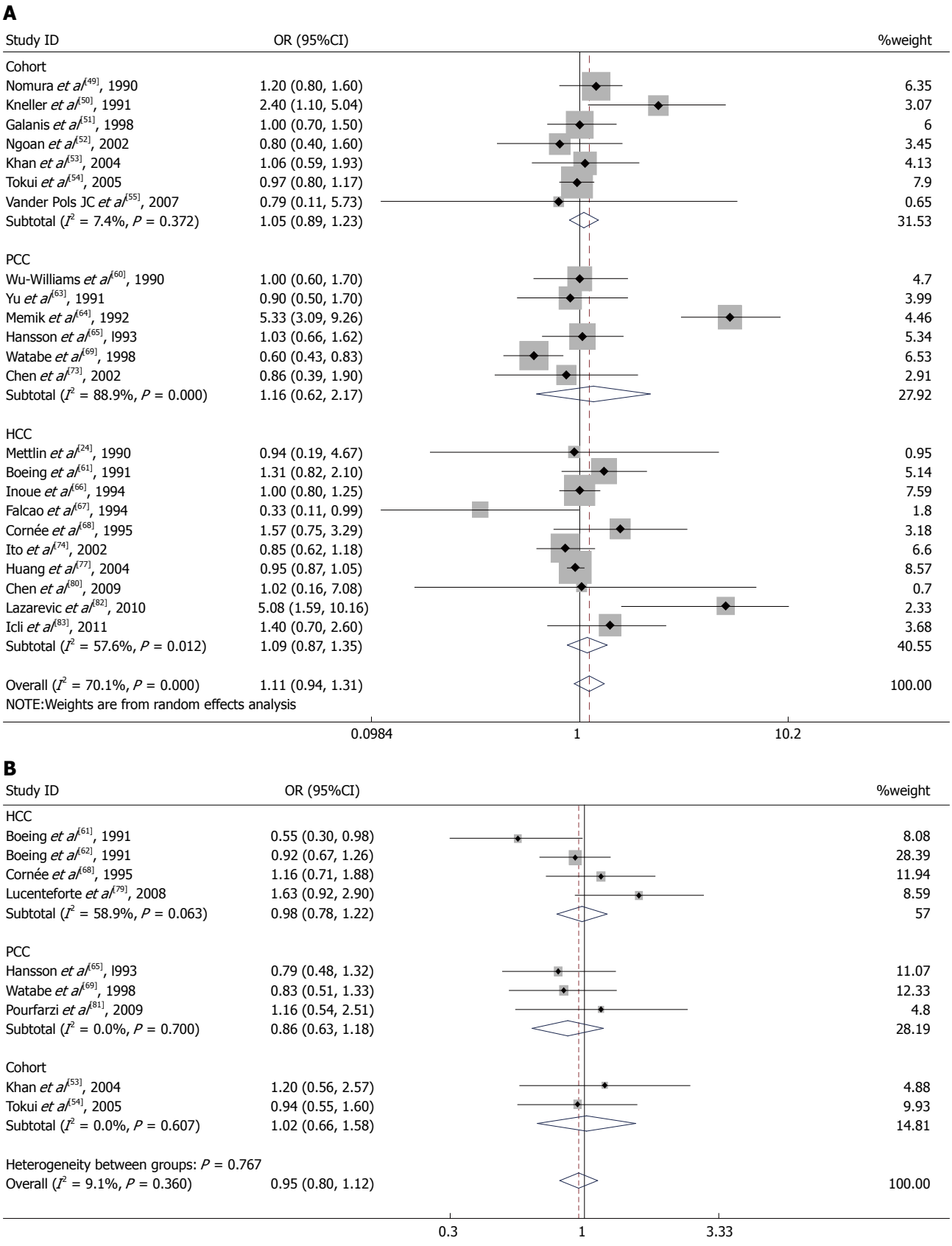

Figure 4 Forest plots of gastric cancer risk associated with milk (A) or cheese (B) consumption, stratified by study design.

cohort studies and 29 case-control studies. Second, we conducted a comprehensive search of the literature on the association between dairy product consumption and gastric cancer risk. Third, our research included a large sample size (837072 subjects and 11791 cases). Fourth, by using a large number of studies from 1980 to the present, we enhanced our statistical power for examining the association between dairy product consumption and gastric cancer risk. Fifth, our study was not subject to publication bias such that the probability of publishing a study did not rely on the strength and direction of the association.

Despite these strengths, our meta-analysis has some limitations. First, we calculated the gastric cancer RR according to the highest *vs* lowest dairy product consumption; as a result, we could not evaluate associations between different dairy product consumption levels and gastric cancer risk. Second, because we could only collect data from published investigations, we did not include any relevant unpublished data, which may affect our results. Moreover, we limited our study to assessing studies that were published in English. Third, the majority of studies reported in this meta-analysis utilized a case-control design, which is more susceptible to recall and selection biases than a cohort design. Fourth, most of studies in our meta-analysis provided RR estimates that were adjusted for a common set of variables (age, sex, and body mass index), but none of the studies could fully adjust for all confounders. For example, infection with *H. pylori* is a known risk factor for gastric noncardia cancer[90]. In our meta-analysis, only two case-control studies[81,84] were adjusted for *H. pylori*. Fifth, heterogeneity may be introduced through the methodological differences among the studies, including different intake measurements. Additionally, because most of the studies presented here used food-frequency questionnaires, the results were likely to be affected by misclassification of dairy product consumption. Sixth, few studies were designed to investigate the risk of gastric cancer from dairy product consumption. Seventh, the studies included in our meta-analysis were only conducted in United States, Europe, and Asia, which limits the findings to the studied populations. Thus, studies of other populations are warranted to generalize our findings.

In conclusion, dairy product consumption was associated with a nonsignificantly increased risk of gastric cancer. However, this result should be verified using large, well-designed prospective cohort and case-control studies, especially in Africa. Future studies should control for more potential confounders, especially for confounders with known gastric cancer risks. In addition, further investigation is warranted to determine whether the effect of dairy product consumption varies by gastric cancer type.

COMMENTS

Background

Gastric cancer remains the fourth most common cancer and the second leading cause of cancer-related mortality. It has recently become popular to analyze the risk factors that may be associated with gastric cancer. Some meta-analyses have found that the risk of gastric cancer is associated with processed meat and coffee, and some meta-analyses have reported that dairy product consumption could increase the risk of ovarian and prostate cancers. It remains unclear whether dairy product consumption is a risk factor for gastric cancer.

Research frontiers

Many case-control and cohort studies have researched the association between gastric cancer and dairy product consumption, but the conclusions have been inconsistent. Therefore, the authors performed a meta-analysis to analyze this association.

Innovations and breakthroughs

In this study, the authors found that dairy product consumption was associated with a nonsignificantly increased risk of gastric cancer. To the best of our knowledge, this is the first meta-analysis to report an association between dairy product consumption and gastric cancer risk.

Applications

This study may offer new insight into gastric cancer prevention. The authors observed that the gastric cancer risk is not significantly related to dairy product consumption. However, this result should be verified using large and well-designed studies, especially in Africa. An exploration of the mechanism for this association will be conducted with a future animal experiment.

Terminology

A meta-analysis is a method for explaining the association between two factors. We collected as much case-control and cohort study data as possible to expand our sample size and obtain a more creditable result. Subgroup analyses were used to investigate the reasons for heterogeneity.

Peer review

This paper is potentially interesting since it deals with a very interesting issue in gastroenterology, as well as in public health medicine. This is a well written article in spite of heterogeneity of data of relevant articles. This issue is important and the work is well conducted.

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