Dairy consumption and liver cancer risk: A meta-analysis of observational studies

JIAYING DAI[1], TONG YIN[2] and LIYING CAO[1]

[1]Department of Hepatobiliary Surgery, KaiLuan General Hospital, North China University of Science and Technology;
[2]Department of Ultrasound, North China University of Science and Technology Affiliated Hospital,
North China University of Science and Technology, Tangshan, Hebei 063000, P.R. China

Abstract. The connection between the consumption of dairy products and the risk of developing primary liver cancer (PLC) remains unclear. The present study performed a comprehensive meta-analysis with the aim of providing evidence for any connection between the risk of developing PLC and the consumption of dairy products. For this purpose, eligible studies were screened from the PubMed, Cochrane Library and Embase databases before December 2022. A total of 10 cohort studies and 8 case-control studies were included, making a total of 18 studies with 6,562,714 participants and 7,970 PLC cases. The relative risks (RRs) for milk and yogurt were 1.38 [95% confidence interval (CI), 1.07-1.77] and 0.49 (95% CI, 0.27-0.91), which revealed a positive and negative association, respectively, with the risk of developing PLC. There was no association between total dairy (RR, 1.04; 95% CI, 0.84-1.30) or cheese and curd (RR, 1.05; 95% CI, 0.87-1.27) consumption and the risk of developing PLC. On the whole, the findings of the present study demonstrated that high milk consumption was associated with a higher risk of developing PLC, while by contrast, yogurt consumption was associated with a lower risk of developing PLC. Consequently, further studies are required to further examine this association.

Introduction

The burden of cancer incidence and mortality is increasing rapidly worldwide. Primary liver cancer (PLC) is ranked sixth most common among all cancer types worldwide, with 905,677 new cases recorded in 2020, while among the leading causes of cancer-related mortality, it is ranked third, with 830,180 cases in 2020 (1). The association between dietary factors and the risk of developing cancer is receiving increasing attention. The majority of dietary guidelines worldwide recommend that individuals should consume dairy products. Some studies have reported the protective role of the consumption of dairy products in breast and colorectal cancer (2,3). However, it has also been reported that the consumption of dairy products may increase the risk of developing prostate cancer (4). These results indicate that the consumption of dairy products may exert differential effects on different cancer sites.

Some studies have explored the association between the risk of developing PLC and the consumption of dairy products in the general population (5,6); however, the connection between the two is not consistent. Previously, two meta-analyses conducted on dairy product consumption and the risk of developing PLC did not reveal any substantial connection. However, one of the meta-analyses only included three cohort studies associated with PLC (5). Although the other meta-analysis included 15 studies, satisfactory results were still not reported (6).

The present study performed a comprehensive meta-analysis to systematically evaluate the association between the risk of developing PLC and the consumption of dairy products, including milk, yogurt, cheese and curd. In addition, subgroup analyses stratified by design, location, duration, size, quality and adjustment factors were conducted.

Materials and methods

Publication search and study selection. A search was performed in the literature for eligible studies published until December 2022 using the PubMed (https://pubmed.ncbi.nlm.nih.gov/), Cochrane Library (https://www.cochranelibrary.com/) and Embase (www.embase.com). The search terms were as follows: '(dairy OR milk OR yogurt OR cheese OR curd)' AND '(primary liver cancer OR primary liver carcinoma OR hepatocellular carcinoma OR HCC)'. Studies were selected by first reviewing the titles and abstracts, followed by screening the full text of the studies that were not excluded. The reference lists were also searched for additional related literature. The present meta-analysis included studies which met the following criteria: i) Case-control studies or cohort studies; ii) studies on dairy products, including total dairy

Correspondence to: Professor Liying Cao, Department of Hepatobiliary Surgery, KaiLuan General Hospital, North China University of Science and Technology, 57 East Xinhua Road, Tangshan, Hebei 063000, P.R. China
E-mail: djy18131374430@163.com

product, milk, yogurt, cheese and curd; iii) an outcome of PLC mortality or incidence; and iv) data on hazard ratio (HR), relative risk (RR) and odds ratio (OR) with corresponding 95% confidence intervals (CIs) were available. Studies were excluded if they met the following conditions: i) Non-human experiments; ii) duplicate studies; iii) reviews, editorials, comments, letters, reports, interviews or studies published in languages other than English; or iv) studies with incomplete data.

Data extraction. The investigators extracted data independently, according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses statement (7). For each study, the following information was obtained: The author's last name, year of publication, location, follow-up period, design, patient sex, size of study, the quantity of cases, dietary assessment, diagnosis approach, outcome, HR or RR or OR with 95% CI values for the connection between the consumption of each dairy product and the risk of developing PLC, and adjusted factors.

Quality assessment. The Newcastle-Ottawa Scale was used to estimate the quality of studies in the present meta-analysis (8). Each satisfactory answer was worth 1 point, with 9 maximum points. Studies with scores of ≥6 points were considered of high methodological quality, and those with scores of <6 points were considered of low quality.

Statistical analysis. The DerSimonian and Laird random-effects models were used to estimate pooled RR and 95% CI values of the risk of developing PLC for the highest compared with the lowest consumption of each type of dairy product, which included total dairy, milk, yogurt, cheese and curd (9), in each included study. Subgroup analyses layered by design (cohort/case-control), location (USA/Europe/Asia), duration (≥5 years/<5 years), size (≥1,500/<1,500) and quality (low/high) were conducted. In addition, it was examined whether the studies had considered for key confounders such as alcohol, smoking, body mass index (BMI), physical activity, diabetes, energy intake, liver diseases or viruses, and education. The studies were stratified and analyzed by whether the factors of alcohol, smoking and BMI were all considered, if all three were considered, it is defined as using strong adjustments, otherwise weak adjustments were used. Heterogeneity was assessed by the I^2 statistic (10). Sensitivity analyses were conducted by excluding each dataset one at a time. The Begg's (11) and Egger's (12) tests were conducted to assess possible publication bias. A two-sided P-value of <0.05 was regarded to indicate a statistically significant difference. Stata/MP 14.0 was used for the statistical analyses.

Results

Characteristics of the included studies. A total of 18 studies (13-30) with 6,562,714 (ranging from 135 to 3,849,637) participants and 7,970 (ranging from 13 to 3,191) PLC cases were included in the present study (Fig. 1). The characteristics of the included studies are presented in Table I. In total, 10 studies were cohort studies (13-22) and eight studies were case-control studies (23-30). Notably, three studies were conducted in the

USA (19,21,22), six studies in Europe (12,16,26-28,30) and nine studies in Asia (14,15,17,18,20,23-25,29). The follow-up period of the studies contained ranged from 2 to 32 years, with the follow-up in 10 studies being ≥5 years (13-17,19-22,25). The majority of studies adjusted for alcohol consumption (n=13) (13-16,19,21-24,27-30), 10 studies adjusted for smoking consumption (13-16,19,22-24,27,28), and eight studies adjusted for BMI (13-16,19,21,22,24). With regard to quality assessment, the studies included in the present meta-analysis had an average score of 6.5 on a 9-point scale; even though four studies had scores <6 (17,18,21,28), which indicates a low quality, other studies had a scores ≥6, indicating a high methodological quality.

Total dairy consumption and the risk of developing PLC. A total of five cohort studies and two case-control studies with eight datasets, including 2,196,482 participants and 5,505 PLC cases, investigated the connection between total dairy consumption and the risk of developing PLC. The summary RR for the highest compared with the lowest total dairy intake was 1.04 (95% CI, 0.84-1.30) with significant heterogeneity among the studies (I^2=93.3% P<0.001; Table II and Fig. 2). Sensitivity analyses revealed no visible difference, irrespective of which dataset was excluded. No effective connections were revealed when stratified by location, quality or adjustment for covariates, and meta-regression analysis detected no effective connections (P-difference ≥0.05 for all contrasts). According to the study design, duration and study size, pooled RRs were 1.21 in the cohort studies, ≥5 years and ≥1,500 groups (95% CI, 1.04-1.40), and 0.58 in the case-control studies, <5 years and <1,500 groups (95% CI, 0.44-0.76). A significant contrary connection was discovered in the cohort studies, ≥5 years and ≥1,500 groups; six studies were contained in this analysis (P-difference=0.006).

Milk consumption and risk of developing PLC. The connection between milk consumption and the risk of developing PLC was evaluated in six case-control studies and six cohort studies with 13 datasets, including 4,615,791 participants and 2,151 cases. The pooled RR for the highest consumption compared with the lowest was 1.19 (95% CI, 0.88-1.62), with moderate heterogeneity among the studies (I^2=70.2, P<0.001; Table II and Fig. 3). An increased risk of developing PLC was observed in the cohort studies (RR, 1.26; 95% CI, 1.02-1.56), but not in the case-control studies (RR, 0.93; 95% CI, 0.44-1.96). With regard to duration, a significant association was observed for ≥5 years (RR, 1.40; 95% CI, 1.07-1.82), but not for <5 years. With regard to the size of the studies, a size ≥1,500 exhibited a significant association (RR, 1.26; 95% CI, 1.02-1.56). Studies that used strong adjustments were associated with an increased risk (RR, 1.32; 95% CI, 1.03-1.68), but not those that used weak adjustments. There were no effective connections when the analysis was stratified by location or quality, and meta-regression analysis revealed no significant discrepancy (P-difference ≥0.05 for all comparisons). In the sensitivity analysis, a significant association was found between the highest compared with the lowest consumption when the study by Talamini in 2006 (30) was removed (RR, 1.38; 95% CI, 1.07-1.77) (I^2=54.2%, P=0.013); however, no significant
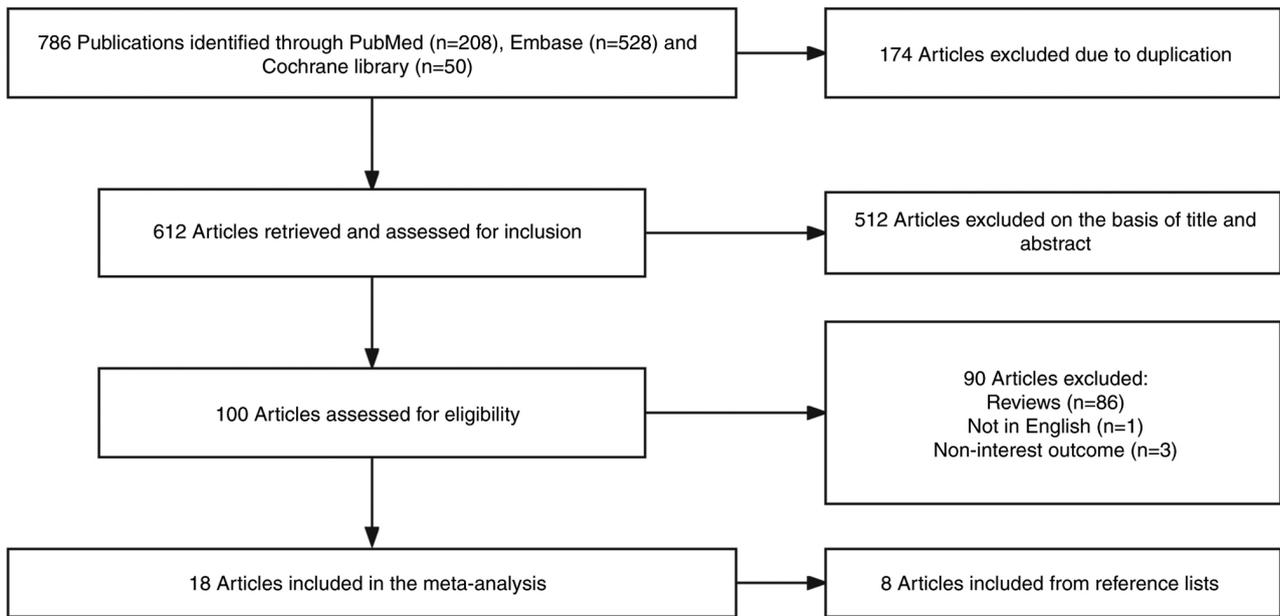
Figure 1. Flow diagram of the literature selection.
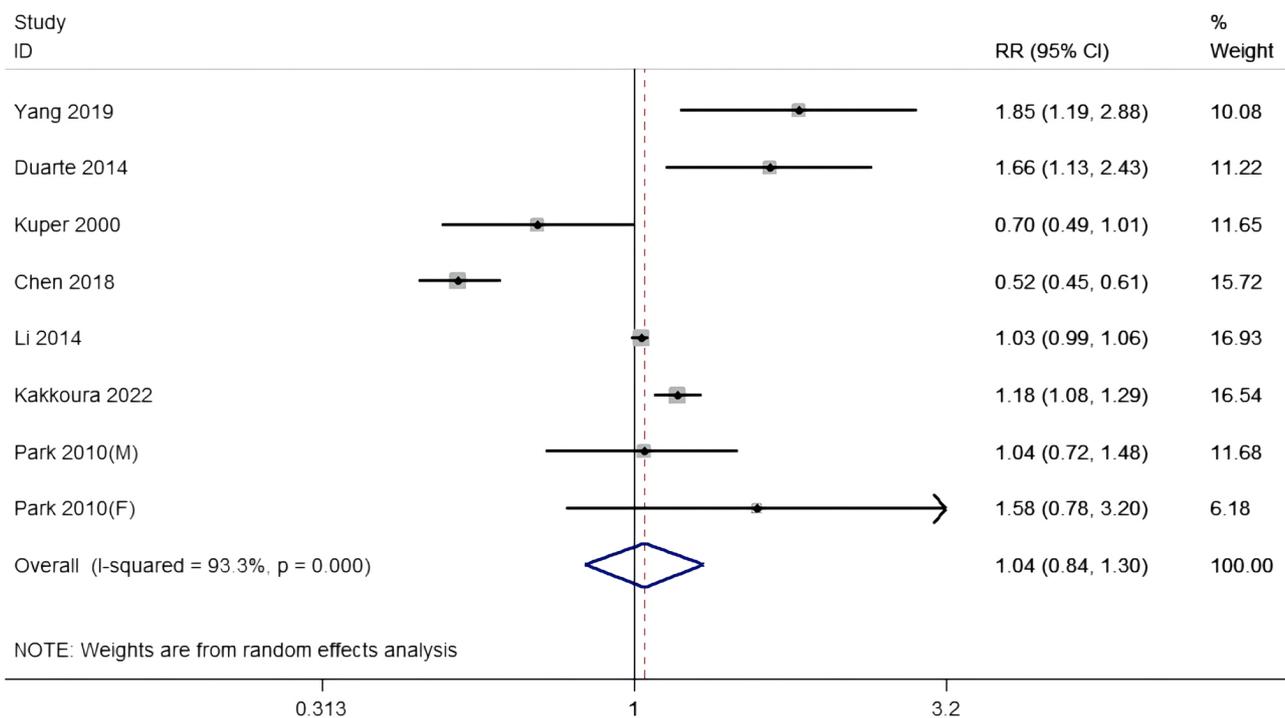
Figure 2. Forest plot of total dairy consumption (highest vs. lowest) and primary liver cancer risk. RR, relative risk; CI, confidence interval; M, male; F, female.

associations were found with the removal of any of the other studies.

Yogurt consumption and the risk of developing PLC. The connection between yogurt consumption and the risk of developing PLC was evaluated in two cohort studies and two case-control studies, including 622,783 participants and 585 cases. The pooled RR for the highest consumption compared with the lowest was 0.49 (95% CI, 0.27-0.91), and exhibited a high heterogeneity among the studies ($I^2=79.5\%$,

P=0.002; Fig. 4). The results of sensitivity analysis were stable. Further subgroup and meta-regression analyses were not executed, as only four studies were included in this sector.

Cheese and curd consumption and the risk of developing PLC. The association between cheese or curd consumption and the risk of developing PLC was assessed in six studies, including 995,483 participants and 1,358 cases. The pooled RR for all studies was 1.05 (95% CI, 0.87-1.27), and exhibited no heterogeneity ($I^2=0.0\%$, P=0.436; Fig. 5). No subgroup or

Table I. Characteristics of studies included in the Meta-analysis on the dairy product intake and liver cancer risk.

First author, year	Location	Duration, years	Design	Patient sex	Study size, n	No. of cases	Dietary assessment	Diagnostic method	Outcome	Exposures: RR (95% CI)	Adjusted variables	Quality score	(Refs.)
Yang et al, 2019	USA	32	Cohort	Both	144,845	164	FFQ-131 items	Histopathology	HCC incidence	Total dairy products: 1.85 (1.19-2.88) Milk: 1.23 (0.83-1.83) Yoghurt: 0.72 (0.49-1.05) Total cheese: 0.88 (0.59-1.31)	Age, sex, ethnicity, physical activity, BMI, smoking, alcohol, total coffee intake, total calorie intake, aspirin use, type 2 diabetes	6	(22)
Duarte et al, 2014	Europe	20	Cohort	Both	477,206	191	Validated questionnaire	Histology	HCC incidence	Total dairy products: 1.66 (1.13-2.43) Total milk: 1.51 (1.02-2.24) Cheese: 1.56 (1.02-2.38) Yoghurt: 0.94 (0.60-1.35)	Age, sex, physical activity, BMI, smoking, self-reported diabetes status, alcohol, energy	7	(16)
Phukan et al, 2018	India	2	Case-control	Both	208	104	Questionnaire	Histopathology/ AFP/angiogarphy/ sonography/liver/ tomography scan	HCC incidence	Milk: 0.09 (0.01-0.71) Curd: 1.32 (0.22-7.83)	Age, sex, location, alcohol, ethnicity	8	(29)
Talamini et al, 2006	Italy	4	Case-control	Both	597	185	Validated FFQ	Histology/ cytology/ ultrasound/ tomography/AFP	HCC incidence	Milk and yoghurt: 0.28 (0.13-0.61) Cheese: 1.31 (0.28-2.96)	Age, sex, centre, education, place of birth, drinking habits, maximal lifetime alcohol intake, hepatitis viruses and total energy intake	7	(30)

Table I. Continued.

First author, year	Location	Duration, years	Design	Patient sex	Study size, n	No. of cases	Dietary assessment	Diagnostic method	Outcome	Exposures: RR (95% CI)	Adjusted variables	Quality score	(Refs.)
Kuper et al, 2000	Greece	4	Case-control	Both	734	333	Validated FFQ	Biopsy/AFP/ echotomography/ other methods	HCC incidence	Milk and dairy products: 0.70 (0.49-1.01)	Age, sex, schooling, infection with HBV and/or HCV, alcohol, smoking, total energy intake, the other food groups	8	(27)
Park et al, 2010	USA	7	Cohort	Both	567,169	397	FFQ-124 items	Registry	Primary liver cancer incidence	Dairy foods: Male, 1.04 (0.72-1.48); female, 1.58 (0.78-3.20)	Ethnicity, education, marital status, BMI, family history of cancer, physical activity, menopausal hormone therapy use, alcohol, intake of red meat, total energy and additional variables	5	(21)
Fukuda et al, 1993	Japan	7	Case-control	Both	853	368	Questionnaire	Histology/ angiography/ ultrasonography	HCC incidence	Milk: Male, 1.88 (1.33-2.65); female, 2.63 (1.46-4.72)	Age, sex, residence, time of hospitalization	7	(25)
La Vecchia et al, 1988	Italy	4	Case-control	Both	1,202	151	Questionnaire	Histology/AFP	HCC incidence	Milk: 0.57 (0.10-3.27)	Age, sex, residence, education, history of hepatitis, alcohol and smoking	5	(28)

Table I. Continued.

First author, year	Location	Duration, years	Design	Patient sex	Study size, n	No. of cases	Dietary assessment	Diagnostic method	Outcome	Exposures: RR (95% CI)	Adjusted variables	Quality score	(Refs.)
Yu *et al*, 2002	China	3	Case-control	Both	496	248	Questionnaire	AFP/ ultrasonogra phy/ CT/liver function tests/angiography	HCC incidence	Milk: 0.69 (0.15-3.09)	Age, sex, residence, alcohol, smoking, HBV	7	(23)
Hirayama, 1989	Japan	17	Cohort	Both	3,849,637	151	Registry	AFP/liver function test/biopsy/image	Primary liver cancer incidence	Milk: 0.93 (0.64-1.35)	Age, sex	4	(17)
Kurozawa *et al*, 2004	Japan	3	Cohort	Both	110,792	401	FFQ-33 items	Death certificates	HCC mortality	Milk: 1.79 (1.14-2.80)	Age, sex, history of liver diseases	5	(18)
Matsumoyo *et al*, 2007	Japan	10	Cohort	Both	11,606	13	FFQ-30 items	Death certificates	Primary liver cancer mortality	Milk: 0.83 (0.27-2.54)	Age, sex	6	(20)
Chen *et al*, 2018	China	4	Case-control	Both	1,440	720	FFQ-79 items	Biopsy/CT/MRI/ AFP	Primary liver cancer incidence	Dairy: 0.52 (0.45-0.61)	Age, sex, BMI, physical activity, education, household income, smoking, alcohol, diabetes, HBV infection, total energy	7	(24)
Kanazir *et al*, 2010	Serbia	4	Case-control	Both	135	45	Questionnaire	Registry	HCC incidence	Milk: 2.10 (0.90-4.60) Cheese: 1.10 (0.47-3.30) Yoghurt:	Age, sex, residence, occupation, birth history, HCV or HBV virus, family history, occupation	7	(26)

Table I. Continued.

First author, year	Location	Duration, years	Design	Patient sex	Study size, n	No. of cases	Dietary assessment	Diagnostic method	Outcome	Exposures: RR (95% CI)	Adjusted variables	Quality score	(Refs.)
Li et al, 2014	USA	12	Cohort	Both	494,942	509	FFQ-124 items	Registry	HCC incidence	Dairy: 1.03 (0.99-1.06)	Age, sex, BMI, ethnicity, smoking, alcohol, activity, education, diabetes	8	(19)
Kakkoura et al, 2022	China	10.8	Cohort	Both	510,146	3,191	Questionnaire	Registry	HCC incidence	Dairy: 1.18 (1.08-1.29)	Education, income, smoking, alcohol consumption, total physical activity, family history of cancer, fresh fruit consumption, soy consumption and BMI	6	(14)
Wang et al, 2020	China	11.5	Cohort	Both	18,214	130	Questionnaire	Registry	Primary liver cancer mortality	Milk: 1.18 (0.72-1.93)	Sex, age, family income, education, occupation, smoking status, alcohol use, physical activity, body mass index, self-rated health, diabetes, hypertension and hyperlipidemia, daily dietary energy intake and dietary quality	7	(15)
Guo et al, 2022	UK	12	Cohort	Both	372,492	669	Questionnaire	Registry	HCC incidence	Cheese: 0.95 (0.72-1.24)	Age, sex, ethnicity, education level, Townsend Deprivation Index (quartiles), drinking status, smoking status, exercise, BMI, diabetes	7	(13)

FFQ, food frequency questionnaire; AFP, α-fetoprotein; CT, computed tomography; MRI, magnetic resonance imaging; HCC, hepatocellular carcinoma; RR, relative risk; CI, confidence interval; BMI, body mass index; HBV, hepatitis B virus; HCV, hepatitis C virus.

Table II. Pooled RRs of PLC risk for the highest compared with lowest dairy consumption.

A, Total dairy

Characteristic	Studies, n	RR (95% CI)	Heterogeneity		P-difference
			I^2, %	P-value	
All studies	8	1.04 (0.84-1.30)	93.3	<0.001	
Design					
Cohort	6	1.21 (1.04-1.40)	76.0	0.001	
Case-control	2	0.58 (0.44-0.76)	54.7	0.138	0.006
Location					
USA	4	1.22 (0.93-1.61)	62.9	0.044	0.519
Asia	2	0.79 (0.35-1.75)	98.8	<0.001	
Europe	2	1.08 (0.46-2.51)	90.3	0.001	0.838
Duration, years					
≥5	6	1.21 (1.04-1.40)	76.0	0.001	0.006
<5	2	0.58 (0.44-0.76)	54.7	0.138	
Size, n					
≥1,500	6	1.21 (1.04-1.40)	76.0	0.001	
<1,500	2	0.58 (0.44-0.76)	54.7	0.138	0.006
Quality					
Low	2	1.14 (0.81-1.61)	6.5	0.301	
High	6	1.01 (0.79-1.29)	95.2	<0.001	0.671
Adjustment for covariates					
Strong adjustment	5	1.07 (0.82-1.41)	96.0	<0.001	0.786
Weak adjustment	3	0.97 (0.65-1.45)	59.1	0.087	

B, Milk

Characteristic	Studies, n	RR (95% CI)	Heterogeneity		P-difference
			I^2, %	P-value	
All studies	13	1.19 (0.88-1.62)	70.2	<0.001	
Design					
Cohort	6	1.26 (1.02-1.56)	20.9	0.276	
Case-control	7	0.93 (0.44-1.96)	81.7	<0.001	0.682
Location					
USA	1	1.23 (0.83-1.83)	-	-	0.735
Asia	8	1.32 (0.90-1.92)	67.4	0.003	0.584
Europe	4	0.90 (0.35-2.32)	82.7	0.001	
Duration, years					
≥5	7	1.40 (1.07-1.82)	56.2	0.033	0.216
<5	6	0.70 (0.28-1.74)	80.1	<0.001	
Size, n					
≥1,500	6	1.26 (1.02-1.56)	20.9	0.276	0.682
<1,500	7	0.93 (0.44-1.96)	81.7	<0.001	
Quality					
Low	3	1.18 (0.67-2.10)	63.9	0.063	
High	10	1.17 (0.80-1.73)	73.5	<0.001	0.997
Adjustment for covariates					
Strong adjustment	3	1.32 (1.03-1.68)	0.0	0.681	0.693
Weak adjustment	10	1.07 (0.68-1.71)	77.2	<0.001	
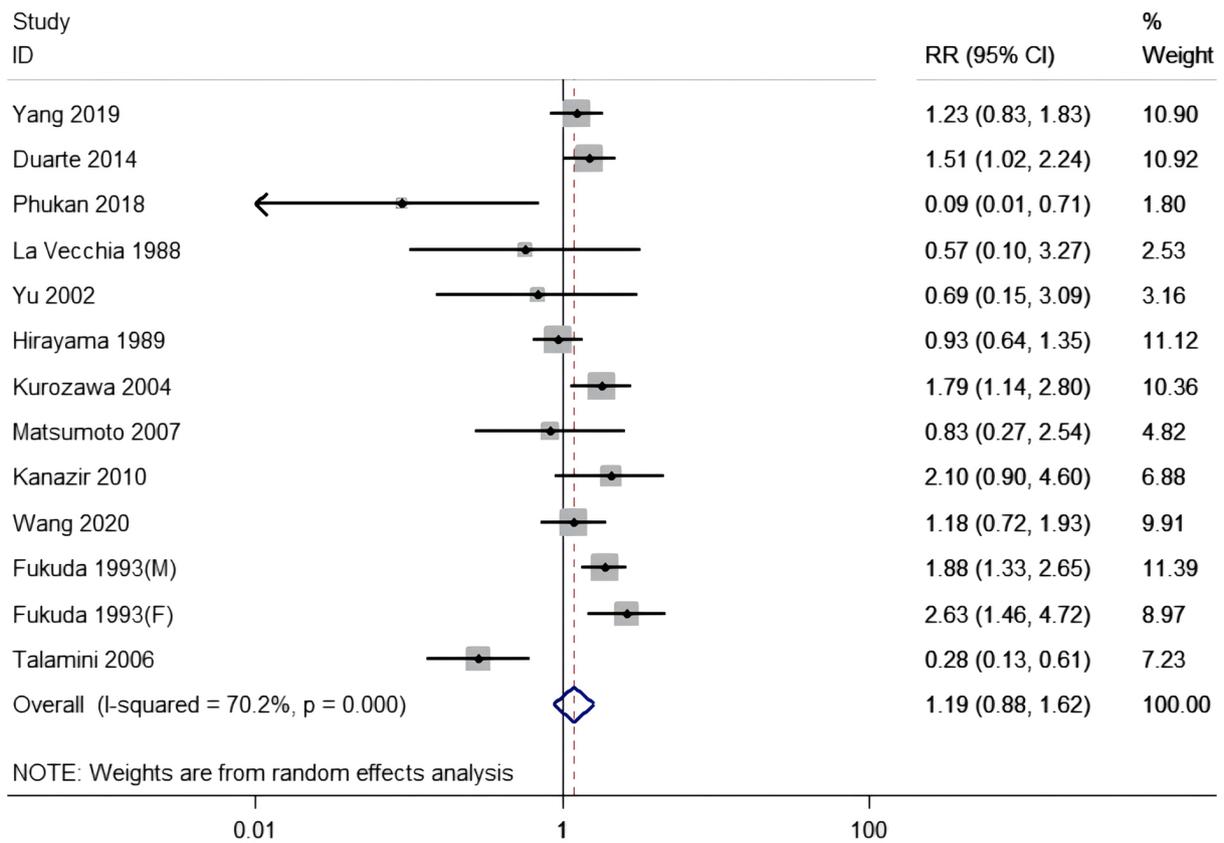
Figure 3. Forest plot of milk consumption (highest vs. lowest) and primary liver cancer risk. RR, relative risk; CI, confidence interval; M, male; F, female.
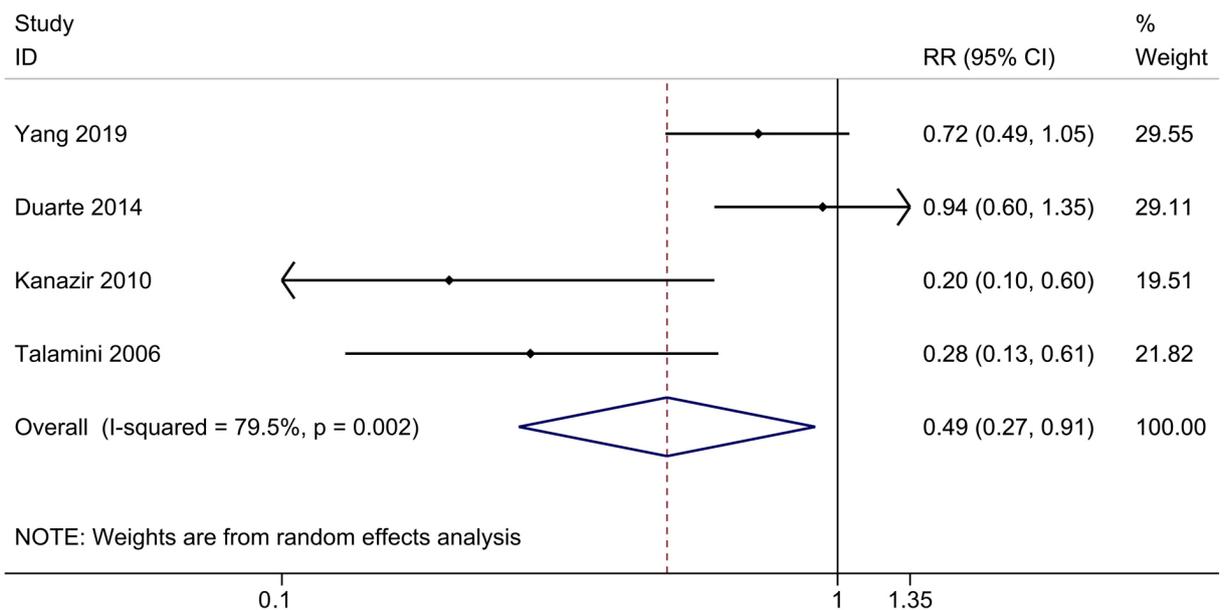
Figure 4. Forest plot of yogurt consumption (highest vs. lowest) and primary liver cancer risk. RR, relative risk; CI, confidence interval.

meta-regression analyses were performed due to the insufficient numbers of studies.

Publication bias. Begg's (P>0.07 in all analyses) and Eggers' tests (P>0.1 in all analyses) of the risk of developing PLC for total dairy and milk consumption revealed no evidence of publication bias.

Discussion

In the present meta-analysis, the potential connections between several types of dairy product consumption and the risk of developing PLC were examined. Compared with a low level of consumption, a high level of milk consumption was related to a higher risk of developing PLC. By contrast, the highest type
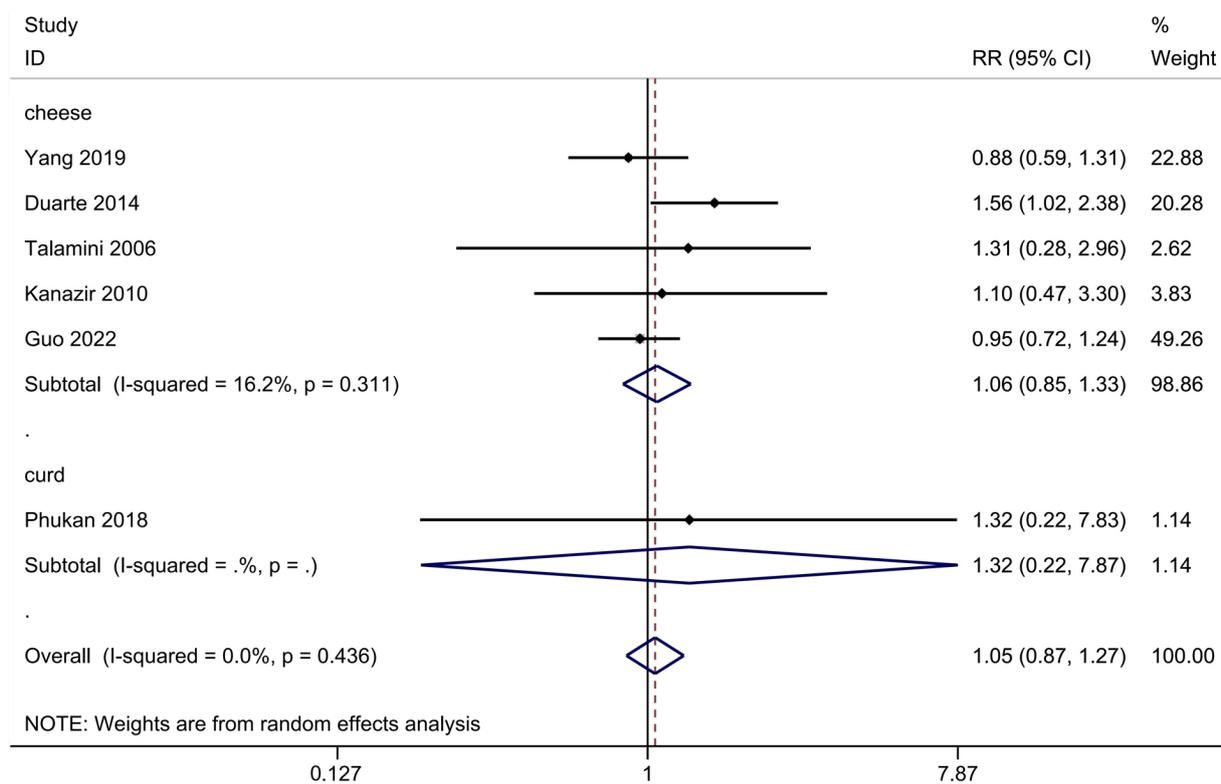
Figure 5. Forest plot of cheese and curd consumption (highest vs. lowest) and primary liver cancer risk. RR, relative risk; CI, confidence interval.

of yogurt consumption was associated with a decreased risk of developing PLC. There was no effective connection between the consumption of total dairy, cheese and curd, and the risk of developing PLC.

Previous meta-analyses have assessed the connection between the risk of developing PLC and the highest compared with the lowest consumption of dairy products (5,6). However, one of the meta-analyses only included studies designed as cohort studies. With regard to milk consumption, the meta-analysis revealed no effective connection between milk consumption and the risk of developing PLC (5). Another meta-analysis reported that yogurt consumption may play a protective role, but revealed no effective connection between the risk of developing PLC and total dairy product, milk, cheese and curd consumption (6). In the present study, the analysis of Zhao *et al* (6) is updated by adding several recent studies on the risk of developing PLC and the consumption of dairy products to further validate these results. The study succeeded in finding a link between high milk consumption and higher PLC risk. The present analysis can therefore provide some implications for the dietary guidelines on milk consumption, promote people to look at milk consumption from a new angle and promote more research related to it.

In the present analysis, it was observed that milk consumption was connected with an increased risk of developing PLC by conducting sensitivity analysis. Talamini *et al* (30) combined milk with yogurt when sorting types of dairy products; with regard to the association of yogurt consumption with the risk of developing PLC, it is possible that the presence of yogurt interfered with the result. Milk, as a health food, plays a critical role throughout the life of an individual. Milk provides essential nutrients and is a main source of natural bioactive

ingredients (31); it is the most abundant and least expensive provider of protein of high nutritional quality, phosphorus, calcium and vitamin A (32). Recent research has reported that the consumption of dairy products appears to be beneficial in building muscle, decreasing blood pressure and low-density lipoprotein cholesterol levels, and preventing tooth decay, cancer, diabetes and obesity (33). With regard to cancer prevention, it has been reported that milk consumption can decrease the risk of developing certain cancer types, such as colorectal, breast and bladder cancer (34), whereas it can increase the risk of developing prostate cancer (4). Milk consumption can increase circulating IGF-I levels (35), and high IGF-I levels have been shown to be associated with an increased risk of cancer, such as prostate and breast cancer (36). The translocation of IGF-I receptor to the endoplasmic reticulum enhances the activity of sarco-endoplasmic reticulum calcium ATPase 2, thus stimulating PLC growth (37). Furthermore, a previous study reported that IGF-1 facilitates the growth and metastasis of hepatocellular carcinoma by inhibiting the degradation of proteasome-mediated cathepsin B (38). Another study reported that IGF-I and branched-chain amino acids from milk can cause PLC by overactivating mTORC1 (39). These are the potential mechanisms by which non-fermented dairy products cause PLC based on the current literature, and further studies are necessary to elucidate the implicated mechanism(s). Although evidence of high heterogeneity among studies was indicated by a meta-analysis of milk consumption and the risk of developing PLC in the present study, the heterogeneity was reduced when classified by the type of cohort, a duration of ≥5 years, a study size of ≥1,500 and strong adjustment for covariates.

Notably, there are still other dietary factors that may affect the statistical results, such as consumption of vegetables, fruits,

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coffee and tea, among others; however, it is not possible to completely control for these dietary factors. Since the objects included in the study were randomly selected, it was assumed that the dietary habits were similar to those in the same location, and a stratified analysis was conducted according to the location to investigate whether they had an impact on the results. The data were also stratified by location, as food safety risks vary by populations of different ethnicities and income levels (40). However, the results obtained did not show any significant difference, so at this time we consider that other dietary consumption does not have significant effect on the conclusion of high milk consumption linking with higher PLC risk. However, the impact of other dietary factors still deserves some attention.

In the present meta-analysis, yogurt consumption was found to be associated with a decreased risk of developing PLC. Yogurt is a nutritious food, as it contains high-quality protein and calcium, as well as other mineral substances, such as iodine, potassium, magnesium, vitamins A and D, and several of the B vitamins (41). Yogurt also contains probiotics, the most common of which are *Lactobacillus* and *Bifidobacterium* (42). Probiotics can enhance the non-specific cellular immune response, which is characterized by activation of macrophages, natural killer cells and antigen-specific cytotoxic T-lymphocytes, and the release of various cytokines, in a strain-specific and dose-dependent manner (43). Zhang *et al* (42) conducted a meta-analysis that demonstrated that yogurt consumption was associated with an overall decreased risk of developing cancer.

The present meta-analysis has several advantages. First, previous epidemiological studies (14,16,22) have clarified the connection between the consumption of dairy products and the risk of developing PLC. On this basis, the present meta-analysis combined and analyzed the data from these studies, thus providing firm evidence. Second, the meta-regression and subgroup analyses were conducted using the variables of design, location, duration, size, quality and other potential confounding factors, in order to explore the underlying heterogeneity. Third, Begg's and Egger's tests were used, and the results revealed that no publication bias excited in the analysis.

Regardless of these advantages, the present meta-analysis has certain limitations, which should be mentioned. First, the analysis was performed on the basis of observational studies, which cannot completely account for the unmeasured or confounding factors. The present meta-analysis also combined cohort and case-control studies; among these, there may be selection and recall bias in case-control studies. However, due to the limited amount of cohort studies, the case-control studies were not excluded from the meta-analysis. Second, the multivariate adjusted RR was extracted; however, only a few studies had considered key confounding factors, such as physical activity, diabetes, liver disease, liver viruses, energy intake or education. Third, the stratified levels of the highest and the lowest consumption of each dairy product across the studies differed. Fourth, although sex, age and other factors were taken into account when the data was extracted, most of the included literature did not distinguish these for analysis, so the study failed to explore the relationship between these basic characteristics of the population and PLC caused by dairy consumption through subgroup analysis of these potential influencing factors. Furthermore, due to the limited amount of data, only five studies demonstrated an association with cheese and four studies an association with yogurt.

In conclusion, in the present meta-analysis, in comparison with low milk consumption, high milk consumption was found to be associated with an increased risk of developing PLC. However, high yogurt consumption was shown to be associated with a decreased risk of developing PLC. Further well-designed studies are warranted, however, to further analyze the connection between each type of dairy product and the risk of developing PLC.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

JD and TY designed the study and formulated the search strategy. JD performed data collection and statistical analysis, and wrote the original manuscript. TY inspected the literature, and reviewed and edited the manuscript. JD, TY and LC were responsible for data interpretation and critical revision of important content, and have read and approved the final manuscript. JD, TY and LC confirm the authenticity of all the raw data.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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