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REVIEW

Dairy consumption and lung cancer risk: a meta-analysis of prospective cohort studies

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Background: Lung cancer risk is the leading cause of cancer-related deaths worldwide. We conducted a meta-analysis to evaluate the relationship between dairy consumption and lung cancer risk.

Methods: The databases included EMBASE, Medline (PubMed), and Web of Science. The relationship between dairy consumption and lung cancer risk was analyzed by relative risk or odds ratio estimates with 95% confidence intervals (CIs). We identified eight prospective cohort studies, which amounted to 10,344 cases and 61,901 participants.

Results: For milk intake, relative risk was 0.95 (95% CI: 0.76–1.15); heterogeneity was 70.2% (P=0.003). For total dairy product intake, relative risk was 0.96 (95% CI: 0.89–1.03), heterogeneity was 68.4% (P=0.004).

Conclusion: There was no significant association between dairy consumption and lung cancer risk.

Keywords: lung cancer, meta-analysis, milk, dairy products

Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide. According to recent estimates, lung cancer causes 1.1 million deaths each year.[1,2] In spite of scientific and medical advances in this area, the survival rate of patients with lung cancer has not significantly improved. Therefore, it is crucial to identify lung cancer risk factors to develop and establish preventive strategies.

Researchers have also focused on the effects of diet and on cancer development.[3] Studies have shown that fruits, vegetables,[4–8] and green tea[9] have anticancer effects. However, other studies have not found any associations.[10] The consumption of dairy products may play a significant role in tumorigenesis. Several meta-analyses have reported an association between dairy consumption and cancer risk, especially of the prostate and breast.[11–13] Epidemiological studies[6,14–20] examining the relationship between dairy consumption and lung cancer risk have produced conflicting results; four studies have reported positive associations with milk[14–16,20] and another four with total dairy products,[15–17,19] while two have reported negative associations with milk[18,20] and another three with total dairy products.[6,17,18] Given that the association between dairy consumption and lung cancer risk remains unclear, we conducted a meta-analysis[21] to assess the relationship between dairy consumption and lung cancer risk. However, the association between dairy consumption and lung cancer risk is unknown and needs to be defined.

Methods

Study search strategy

We designed and performed a meta-analysis based on the Meta-Analysis Guidelines for epidemiological observational studies.[22] The databases included EMBASE, Medline

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(PubMed), and Web of Science. The studies reviewed included case–control and cohort studies that evaluated the relationship between dairy consumption and lung cancer risk. The search terms were lung cancer, lung carcinoma, milk, dairy products, and total dairy foods.

Inclusion criteria

The inclusion criteria were: 1) human clinical trials published in English; 2) studies where dairy product consumption was the main exposure; 3) studies that presented the odds ratio (OR) or relative risk (RR) with 95% confidence interval (CI); and 4) prospective cohort studies.

Data extraction and quality assessment

The data extracted from the studies included the first author, year of publication, average follow-up time, study region, exposure time, number of cases, population characteristics, adjusted ORs, RRs, or hazard ratio (HR) with their 95% CIs and adjustments. Four publications[6,15,16,19] reported separate RRs for different dairy products; therefore, the RR estimates with the maximum number of cases within each study were selected.

To assess the quality of the study designs, we evaluated key components of the studies.[22] We used Q and I^2 statistics to estimate heterogeneity among the studies; any disagreements were resolved by discussion.

Data analyses

The association between total dairy product or milk consumption and lung cancer risk was assessed by RRs. Milk included whole/high-fat milk and skim/low-fat milk; total dairy products included cheese, ice cream, artificial butter, butter, margarine, yoghurt, and other dairy products. Where crude and adjusted RRs were provided, we used the adjusted RRs.

The incidence of lung cancer in humans is low; therefore, the ORs were deemed to be equal to HRs and RRs. RRs and 95% CIs were estimated based on adjusted RRs or ORs for the highest versus the lowest dairy product intake.

We used Q ($P \leq 0.10$) and I^2 statistics to examine the homogeneity across studies[23] and the fixed effects model when substantial heterogeneity was detected.[24] Subgroup analyses were conducted on cases $\geq$300; subgroup analysis was performed when adjusting for smoking status and age. Additionally, we investigated the effect of a single study on the overall risk estimate.

Data analyses were performed with STATA version 12.0 (StataCorp LP, College Station, TX, USA). $P<0.05$ was considered to be statistically significant. We used Egger's linear regression and Begg's rank correlation methods to evaluate potential publication bias.[25,26]

Results

Studies

Figure 1 illustrates detailed steps of study selection. A total of eight studies were included in our meta-analysis.

Study characteristics

The characteristics of the eight studies are presented in Table 1. The studies were published in 1996–2014. Six

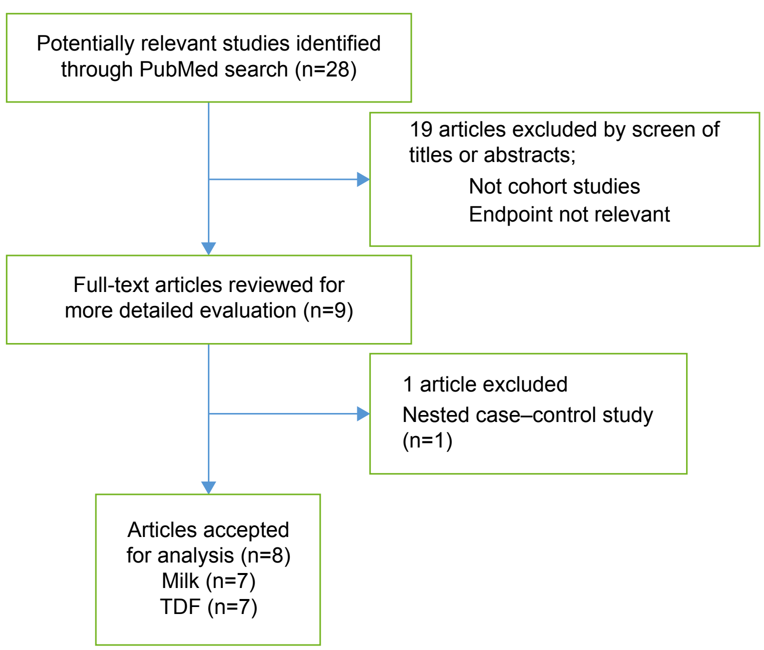

Figure 1 Search strategy and selection of studies for inclusion in the meta-analysis.
Abbreviation: TDF, total dairy food.

Table 1 Characteristics of the eight prospective cohort studies included in the meta-analysis

Reference	Population	Duration (years)	No of cases	Assessment	Exposure	Consumption levels	OR or RR (95% CI)	Adjustment for potential confounders
Axelsson et al[14]	1,286; age: ≤75 years; Scandinavian	4	308	Q	Milk	High vs low	1.73 (1–3.01)	Age, number of cigarettes/day, number of years smoking cigarettes (continuous variables), marital status (four classes) and socioeconomic job classification (seven classes), smoking status, fruit and vegetable consumption
Nyberg et al[15]	479; age: ≥30 years never-smokers; Stockholm	6	124	Q&FFQ	Milk	≥2 vs 0 glasses/day	1.24 (0.71–2.17)	Sex, age, smoking status, residence (urban vs rural), occupational exposure, fruit consumption
			124		TDF	High vs low	1.21 (0.61–2.39)	
Hosseini et al[16]	754; age: ≥75 years; Iran	3	482	Q	Milk	Upper third vs lower third	2.64 (1.54–4.51)	Family history of lung cancer, total energy intake, smoking status, BMI
			482		TDF	Upper third vs lower third	2.94 (1.79–4.82)	
Park et al[17]	53,570 AARP members; age: 50–71 years	7	4,287	Q	TDF	Q5 vs Q1	1.05 (0.95–1.16) (men)	Race/ethnicity, education, marital status, BMI, family history of lung cancer, physical activity, alcohol consumption, red meat intake, total energy intake
			2,457	Q	TDF	Q5 vs Q1	0.92 (0.81–1.04) (women)	Race/ethnicity, BMI, maternal age at first delivery, number of children, age at menopause, education, marital status, family history of lung cancer, physical activity, MHT use, smoking status, and intakes of red meat, alcohol, fat, and total energy
Rachtan[19]	594; median age: 61 years; Cracow	6	242	Q	TDF	High vs low	1.62 (0.94–2.81)	Age, smoking status, alcohol consumption (beer and vodka), siblings with cancer, tuberculosis, place of residence, occupational exposure
Axelsson et al[20]	1,452; lung cancer patients; age: ≤75 years; Scandinavian	5	177	FFQ	Milk	High vs low	1.9 (1.1–3.3) (women)	Age (continuous variable), number of cigarettes smoked per day (four classes), number of years smoking cigarettes (five classes), marital status (four classes), consumption of vegetables, fruits, and milk
		3	359		Milk	High vs low	1.9 (1.3–2.9) (men)	
Brennan et al[6]	1,551; age: 0–75 years	3	496	FFQ	TDF	High vs low	0.7 (0.5–1.0)	Age and sex
			500		Milk	High vs low	0.8 (0.6–1.2)	
Van der Pols et al[18]	2,215; average age: 8 years; United Kingdom	65	153	Q	TDF	≥1.2 vs <0.5 cups/day	0.66 (0.39–1.10)	Age, weight, height, region, season, and intake of total energy, fruits, and vegetables
			153		Milk	>1.2 cups vs <0.5 cup	0.65 (0.40–1.08)	

Abbreviations: BMI, body mass index; CI, confidence interval; FFQ, Food Frequency Questionnaire; Q, quintile; OR, odds ratio; RR, relative risk; TDF, total dairy food; No, number; AARP, American Association of Retired Persons; MHT, menopausal hormone therapy.

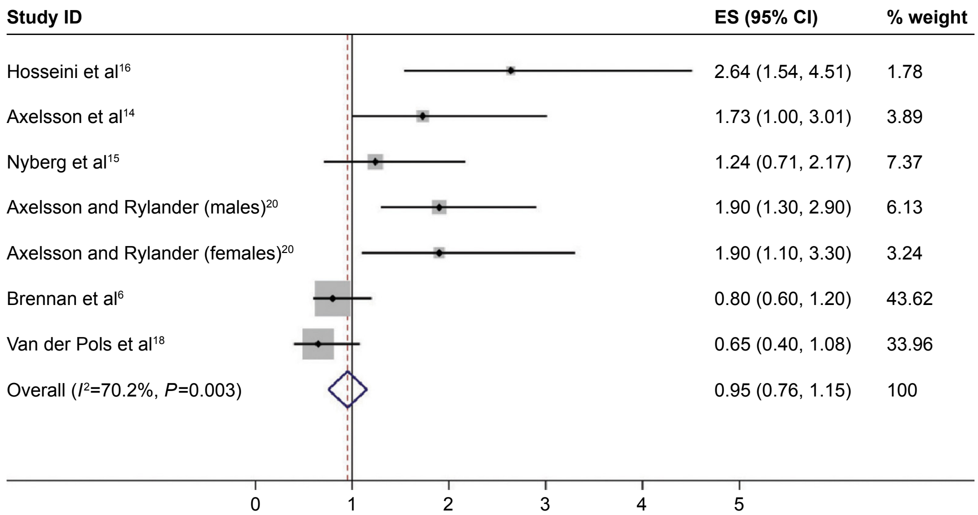

Figure 2 Forest plot of studies examining the association between milk intake and lung cancer risk.
Abbreviations: CI, confidence interval; ES, effect size; ID, identification.

studies were performed in Europe, one was conducted in the USA, and one was performed in Iran. The number of participants varied from 479 to 53,570, with a total of 58,997 subjects, and the lung cancer cases ranged from 124 to 4,287, with a total of 8,857 cases. Among the eight studies, seven reported data on total dairy product intake and seven reported data on milk intake. The follow-up ranged from 3 to 65 years, with a median follow-up of 4.5 years. Most studies were matched or adjusted for family history, body mass index, total energy intake, and age.

Main results

Total dairy intake was inconsistent among seven studies. For the final RR, the highest versus the lowest total dairy consumption was 0.96 (95% CI: 0.89–1.03); heterogeneity was 68.4% (P=0.004). Total milk intake was similarly inconsistent among the seven studies. The final RR was 0.95 (95% CI: 0.76–1.15); heterogeneity was 70.2% (P=0.003). The pooled RRs for the highest versus the lowest total milk intake and total dairy food consumption and lung cancer risk are shown in Figures 2 and 3. Based on the results, there was no significant association between dairy consumption and lung cancer risk.

Subgroup analyses

Table 2 shows the results of the subgroup analyses. We conducted a subgroup analysis for dairy product consumption after adjusting for smoking status and age. For total dairy

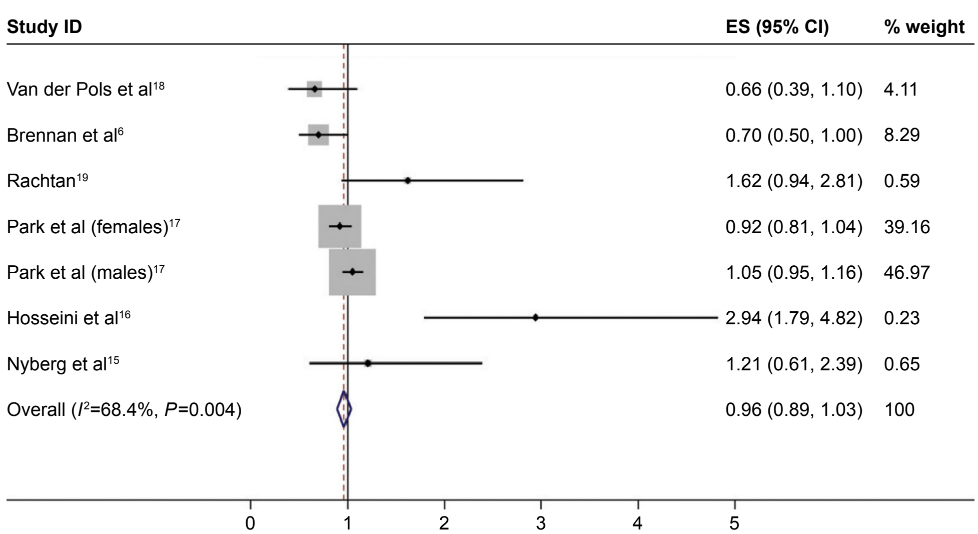

Figure 3 Forest plot of studies examining the association between total dairy product intake and lung cancer risk.
Abbreviations: CI, confidence interval; ES, effect size; ID, identification.

Table 2 RRs of lung cancer in relation to milk and total dairy food consumption

Group	Total dairy food				Milk			
	No of studies	RR (95% CI)	$P_{heterogeneity}$	I^2 (%)	No of studies	RR (95% CI)	$P_{heterogeneity}$	I^2 (%)
Total cases	7	0.96 (0.89–1.03)	0.004	68.4	7	0.95 (0.76–1.15)	0.003	70.2
>300	4	0.97 (0.90–1.04)	0.003	78.5	4	1.05 (0.78–1.31)	0.004	77.2
≤300	3	0.83 (0.52–1.14)	0.115	53.7	3	0.84 (0.54–1.14)	0.052	66.2
Adjustments in models								
Smoking	4	0.95 (0.83–1.06)	0.027	67.3	5	1.71 (1.29–2.13)	0.488	<0.01
Age	4	0.75 (0.56–0.95)	0.191	36.9	6	0.92 (0.72–1.12)	0.010	66.9

Abbreviations: CI, confidence interval; RR, relative risk; No, number.

product and milk consumption, there was no significant association with lung cancer risk. A sensitivity analysis revealed that RR ranged from 0.66 (95% CI: 0.39–1.10) to 2.94 (95% CI: 1.79–4.82) for total dairy food consumption and from 0.65 (95% CI: 0.40, 1.08) to 2.64 (95% CI: 1.54–4.51) for milk consumption.

Discussion

To the best of our knowledge, this is the first meta-analysis to investigate dairy consumption and lung cancer risk. We found that for milk intake, the RR was 0.95 (95% CI: 0.76–1.15) and the heterogeneity was 70.2% (P=0.003). For total dairy product intake, the RR was 0.96 (95% CI: 0.89–1.03) and the heterogeneity was 68.4% (P=0.004). Subgroup analysis for dairy product consumption suggested that there was no significant association with lung cancer risk.

Dairy consumption may play a role in cancer development.[27] However, the evidence from observational studies is inconclusive. The mechanism of any relationship between the consumption of dairy products and the risk of lung cancer remains unclear. There are reports of associations between lung cancer and insulin-like growth factor I,[28,29] poor vitamin D status,[30,31] and polychlorinated biphenyls,[32–34] suggesting possible roles for these factors in tumorigenesis. Previous analyses have led to conflicting findings regarding the association of dairy consumption and lung cancer risk. Two analyses have provided evidence that excess of 25-hydroxy vitamin D may be associated with a reduced risk of lung cancer, especially in subjects with vitamin D deficiency.[35,36]

Our meta-analysis had several strengths. To improve the statistical power, we included several studies, all of which had a prospective cohort design. This design minimizes selection bias and recall, which is a limitation of retrospective studies. However, there were several limitations in our study. The number of studies included was relatively small, and only studies written in English were considered. Additionally, it is possible that there were unexamined or uncontrolled confounding factors in the included studies, for example, smoking, which is known to be an important risk factor for lung cancer.[37–39]

There was heterogeneity across the studies in terms of total dairy product and milk consumption, which is not surprising considering the differences in the study designs and in the study populations. Heterogeneity may also have been a consequence of different durations of exposure to dietary products and different dietary habits.

In conclusion, our meta-analysis, which involved eight studies, revealed no significant association between dairy consumption and lung cancer risk. Large cohort studies were adjusted to take account of potential confounding factors, including total energy intake, body mass index, age, and other dietary factors, which are highly correlated with milk and/or total dairy consumption. Further well-designed studies are required.

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Disclosure

The authors confirm that they were not involved in studies included in the meta-analysis. The authors report no conflicts of interest in this work.

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