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The association between dairy products consumption and prostate cancer risk: a systematic review and meta-analysis

Zifan Zhao[1], Donghong Wu[1], Sirui Gao[1], Dongda Zhou[1], Xiaoying Zeng[1], Yuxuan Yao[1], Yilin Xu[1] and Guohua Zeng[2]*

[1]*Nanshan School, Guangzhou Medical University, Guangzhou 510180, People's Republic of China*
[2]*Department of Urology, Guangdong Key Laboratory of Urology, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou 510230, People's Republic of China*

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Abstract
In this study, we conducted a meta-analysis to estimate the relationship between the consumption of dairy products and the risk of prostate cancer. We searched PubMed, Embase and Cochrane databases for relevant articles and identified a total of thirty-three cohort studies between 1989 and 2020. The qualities of included studies were assessed using Newcastle–Ottawa scale. Pooled adjusted relative risks (RR) with 95 % CI were calculated. We performed subgroup analyses stratified by dairy type, prostate cancer type, follow-up years, treatment era, collection times, adjustment for confounders and geographic location. In the subgroup analysis stratified by prostate cancer type, the pooled RR were 0·98 (95 % CI 0·94, 1·03) in the advanced group, 1·10 (95 % CI 0·98, 1·24) in the non-advanced group and 0·92 (95 % CI 0·84, 1·00) in the fatal group. In the dose–response analysis, a positive association for the risk of prostate cancer was observed for total dairy products 400 g/d (RR: 1·02; 95 % CI 1·00, 1·03), total milk 200 g/d (RR: 1·02; 95 % CI 1·01, 1·03), cheese 40 g/d (RR: 1·01; 95 % CI 1·00, 1·03) and butter 50 g/d (RR: 1·03; 95 % CI 1·01, 1·05). A decreased risk was observed for the intake of whole milk 100 g/d (RR: 0·97; 95 % CI 0·96, 0·99). Our meta-analysis suggests that high intakes of dairy products may be associated with an increased risk of prostate cancer; however, since many of the studies were affected by prostate-specific antigen (PSA) screening bias, additional studies with an adjustment of PSA screening are needed.

Keywords: Dairy products: Prostate cancer: Meta-analysis: Systematic review

Prostate cancer is the second most frequent cancer diagnosis made in men and the fifth leading cause of death worldwide[1]. It is estimated that up to 2040, the worldwide prostate cancer risk will be elevated, with 1 017 712 new cases[2]. Differences in incidence rates were up to 190-fold between the populations at the highest rate (France, Guadeloupe, 189·1/100 000 people) and the populations with the lowest rate (Bhutan, 1·0/100 000 people)[3]. Despite decades of research, the well-established prostate cancer risk factors are limited to advanced age, African ancestry, genetic polymorphisms and family history[1]. With the aetiology of prostate cancer largely unknown, feasible measures for primary prevention of the disease remain limited.

Although the variation in incidence rates across populations can be attributed to differences in diagnostic intensity arising from the practice of prostate-specific antigen (PSA) screening, the evidence of geographic variation in prostate cancer incidence predating the introduction of PSA screening suggests a potential role of lifestyle factors in prostate cancer risk[4]. Some research on migration found an increased prostate cancer incidence in immigrants who move from developing countries to industrialised countries. For example, Hsing *et al.*[5] showed that compared with men living in China, the prostate cancer incidence was 16-fold higher for Chinese men living in the USA. Lee *et al.*[6] also showed that the incidence rate of prostate cancer was 3·5 times higher in US Koreans compared with their native counterparts, while Chu *et al.*[7] reported that the rate among African Americans was as high as forty times when compared with those in Africa. Epidemiological study implicated that the changes in lifestyle, including dietary factors, would induce a shift towards an increased prostate cancer incidence[1]. But to date, few dietary risk factors for prostate cancer have been firmly established[8].

It is estimated that by 2030, the per capita consumption of dairy food would be 65·8 kg in the developing countries and 221·0 kg in the industrialised countries[9]. High correlations between intake of dairy foods and milk and prostate cancer risk have been reported in many ecologic studies[10,11,12], but they are less credible than case–control and cohort studies due to their

Abbreviations: IGF, insulin-like growth factor; PSA, prostate-specific antigen; RR, relative risk.

* **Corresponding author:** Dr G. Zeng, email 2008690094@gzhmu.edu.cn

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evaluation method. Data from observational cohort and case–control studies, however, have been inconclusive and the conclusion about a relationship between dairy product consumption and prostate cancer is more contradictory than in ecological studies.

Meta-analysis is a statistical method that can overcome the problem of limited sample size in the published data and draw stronger or clearer conclusions[13]. In 2005, Gao *et al.*[14] confirmed a positive association of the consumption of dairy products with prostate cancer risk, specifically in men with the highest intakes. The results of a meta-analysis in 2007[15] also supported the previous conclusions. However, in 2008, Huncharek *et al.*[16] pooled eleven cohort studies and found no evidence of an association between dairy intakes and prostate cancer risk. In 2015, a previous meta-analysis investigated dairy intakes and prostate cancer risk[17], suggesting that high intakes of dairy products, milk, low-fat milk and cheese may increase total prostate cancer risk. However, in 2018, the evidence that a higher consumption of dairy products increases the risk of prostate cancer went from 'probable' to 'limited' in the World Cancer Research Fund/American Institute for Cancer Research report[18]. Since 2015, four additional prospective cohort studies evaluating the association between dairy product consumption and prostate cancer risk were published[19-22]. Given the discrepancies observed between the systematic reviews and meta-analysis results, we conducted an up-to-date systematic review and meta-analysis in an attempt to re-evaluate whether dairy product intake could increase the risk of prostate cancer.

Methods

Study strategy

The Meta-analysis Of Observational Studies in Epidemiology guidelines were followed to conduct this meta-analysis. We performed a systematic search of PubMed, Embase and Cochrane databases for relevant studies before March 2021 that assessed the association between dairy products consumption and the risk of prostate cancer, using the following search algorithm: ('Dairy Products' (Mesh) OR 'Dairy Product' OR 'Product, Dairy' OR 'Products, Dairy' OR milk OR yogurt OR cheese OR butter OR ice cream) AND ('Prostatic Neoplasms' (Mesh) OR 'Prostate Neoplasms' OR 'Neoplasms, Prostate' OR 'Neoplasm, Prostate' OR 'Prostate Neoplasm' OR 'Neoplasms, Prostatic' OR 'Neoplasm, Prostatic' OR 'Prostatic Neoplasm' OR 'Prostate Cancer' OR 'Cancer, Prostate' OR 'Cancers, Prostate' OR 'Prostate Cancers' OR 'Cancer of the Prostate' OR 'Prostatic Cancer' OR 'Cancer, Prostatic' OR 'Cancers, Prostatic' OR 'Prostatic Cancers' OR 'Cancer of Prostate') AND ('Cohort Studies' (Mesh)) NOT ('Animal Experimentation' (Mesh) OR 'Case Reports' (Publication Type) OR 'Editorial' (Publication Type) OR 'Review' (Publication Type) OR 'Clinical Trial' (Publication Type)). Two reviewers (ZF Zhao and DD Zhou) evaluated all the potentially relevant publications by examining their titles and abstracts. The full texts of studies that matched the eligible criteria were retrieved. We also performed manual searches according to cited references from retrieved articles and previous reviews on dairy products and prostate cancer. The results were restricted to publications. Any disagreements on study selection were resolved via group discussion.

Study selection

Given that the case–control studies are prone to recall and selection bias, which may lead to the spurious association, we only included the published cohort studies to evaluate the relationship between dietary consumption of dairy products and prostate cancer risk.

Studies were eligible for the meta-analysis if they met the following criteria: (1) cohort design; (2) exposure of interest was dairy consumption (including total dairy, milk, butter, cheese, ice cream, yogurt and other dairy products); (3) outcome was prostate cancer incidence; (4) the estimates of relative risk (RR) or hazard ratio or OR with corresponding 95 % CI were available and (5) the most recent and complete study was selected if data from the same population had been published more than once.

The following types of publications were excluded: (1) abstracts, editorials, reviews, case reports, clinical trials, conference articles and animal studies; (2) studies lacking sufficient available data and (3) articles not written in English.

Data extraction

Following variables were extracted from included articles: first author, publication year, country, study design, follow-up duration, study name, age, sex, outcome assessment, type of dairy product (e.g. total dairy, milk, butter, cheese, ice cream, cream, yogurt), intake of dairy products, outcome assessment, number of cancer case, sample size, adjustment for confounders, adjusted RR, adjusted hazard ratio, adjusted OR and 95 % CI. Data extraction was conducted by three reviewers (ZF Zhao, DD Zhou, SR Gao).

Quality and risk of bias assessment

We used the Newcastle–Ottawa scale to assess the methodological quality and bias of the enrolled studies[23]. Newcastle–Ottawa scale score was categorised into three levels: low, moderate and high quality as the Newcastle–Ottawa scale scores of 0–5, 6–7 and 8–9. Two reviewers (XY Zeng, YX Yao) independently assessed the quality of each study. Any conflicts concerning the assessment were solved through discussion.

Statistical methods

The RR and mean difference with 95 % CI for categorical variables were calculated to investigate the relationship between dairy product intake and prostate cancer risk. When both crude and adjusted RR were provided, we used the most fully adjusted RR for all studies. As the hazard ratio and RR were interchangeable, we used the hazard ratio as RR and converted the OR to RR using a website calculator (https://clincalc.com/Stats/ConvertOR.aspx). Heterogeneity was evaluated using Cochran's Q and I^2 statistics, in which P-value of $< 0{\cdot}1$ and $I^2 > 50\,\%$ were defined as statistically significant heterogeneity. When there existed significant heterogeneity, we used a random-effects model to summarise the test performance; otherwise, a fixed-effects model was used[24]. Subgroup analyses were conducted stratifying by dairy type, prostate cancer type, follow-up years, treatment era, collection times, adjustment for confounders and geographic location. We performed analyses for total prostate cancer, non-advanced, advanced and fatal prostate cancers. For the analysis of non-advanced cancers, we included studies that reported on low-grade, low-stage and localised cancers. Advanced prostate cancers included high-grade, high-stage, non-localised and advanced cancers. Egger's funnel plot was performed to detect the potential publication bias. A two-sided P value of < 0·05 was considered statistically significant. The analyses were conducted using R software (version 3.6.1, https://www.rproject.org/).

We conducted dose–response analyses with the one-stage robust error meta-regression model, based on inverse variance weighted least squares regression and cluster-robust error variances[25]. The method required RR with 95 % CI for at least two levels of dairy exposure reported, but the distribution of cases or person-years was not required. As dairy intakes were heterogeneous, we used the United States Department of Agriculture Food and Nutrient Database for Dietary Studies[26] to estimate the dose of dairy intake when studies reported intakes in servings and times/d or week. We converted intakes to grams of intake/d by using standard units of 244 g (or 244 ml) for milk and yogurt, 43 g for cheese (two slices), 14 g for butter, 135 g for ice cream and 177 g for total dairy products. The median or mean dairy intake in each category of intake was assigned to the corresponding RR for each study when it was reported. The midpoint was calculated for studies that reported a range of intake and did not provide the mean or median intake for the range of dairy intake. When the highest or lowest category was open ended, it was assumed that the open-ended interval length had the same length as the adjacent interval. The analyses were performed using STATA statistical software (version 15.1).

Results

Publication search and study selection

Fig. 1 shows the search strategy and study selection. A total of 1325 relevant publications were identified through PubMed, Embase and Cochrane databases. Of these publications yielded from the literature search, 326 duplicates were removed. The remaining 999 publications were screened based on titles and abstracts. After the exclusion of 912 publications, eighty-seven studies were assessed for eligibility by screening the entire text. Finally, thirty-three articles were included in our study after a review of the full text[19-22,27-55].

Study characteristics

Study characteristics of the thirty-three studies are summarised in Table 1. The studies were published between 1989 and 2020. They were performed in different countries, with twenty-two in the USA[19,20,27-31,35-38,40-44,47-49,53-56], two in the UK[22,50], two in Finland[34,46], one in Norway[32], one in Sweden[21], one in the Netherlands[33], one in France[45], one in multiple countries of Europe[51] and two in Japan[39,52]. Of the thirty-three studies, 177 206 cases were found in 4 212 923 participants. Thirteen studies had a follow-up duration of 10 years or more while twelve studies followed up for less than 10 years. All of the studies were prospective cohorts that met the inclusion criteria. After evaluation of study quality[23], all of the included studies were classified either as high or as moderate quality, with a total of fifteen high quality studies[19,20,31,33,34,36,38-40,45-47,50,53,56] and a further eighteen moderate quality studies[21,22,27-30,32,35,37,41-44,48,49,51,52,54] identified.

Total dairy products

Twenty-six cohort studies[19,20,27,29-32,34-36,38,40-50,52-54,56] investigated total dairy product consumption and prostate cancer incidence and included 110 982 cases in 1 536 556 participants. The summary adjusted RR for highest compared with lowest intake was 1·05 (95 % CI 1·00, 1·09), with moderate heterogeneity (I^2 = 39 %, P-heterogeneity = 0·02). The forest plot and funnel plot are presented in Fig. 2 and 3, respectively. There was no indication of publication bias (Egger's test: P = 0·09 and Begg's test: P = 0·63). In the dose–response analysis, an increase in total dairy intake by 400 g/d was positively associated with the risk of prostate cancer (RR: 1·02; 95 % CI 1·00, 1·03). When total dairy intake was over 500 g/d, the results were insignificant. There was evidence of a nonlinear association between total dairy product intake and prostate cancer risk (P-nonlinearity = 0·03; n 20). The risk of prostate cancer increased by 2 % with increasing the intake of total dairy ≤400 g/d (Fig. 4(a)).

Total milk

Seventeen studies[19,20,28,31-33,37,39,40,43,45,46,48-52] including 32 690 cases were included in the highest compared with lowest intake category meta-analysis (range of intake: 0–840 g/d). In this analysis, we observed a positive association between the risk of prostate cancer and total milk intake (RR: 1·07; 95 % CI 1·00, 1·14; I^2 = 46 %; P-heterogeneity = 0·02) (online Supplementary Fig. 1). Similarly, an increase in total milk intake by 200 g/d was associated with the risk of prostate cancer (RR: 1·02; 95 % CI 1·01, 1·03). When total milk intake was over 400 g/d, the results were insignificant. There was evidence of a nonlinear association between total milk intake and prostate cancer risk (P-nonlinearity < 0·01; n 16). The risk of prostate cancer increased by 2 % with increasing the intake of total dairy ≤300 g/d (Fig. 4(b)).

Whole milk

Seven studies[19,27,29,40,48,54,56] with 12 929 prostate cancer cases were included in the meta-analysis comparing extreme intake categories (range of intake: 0–668 g/d). An inverse association between the risk of prostate cancer and whole milk intake was observed (RR: 0·93; 95 % CI 0·87, 0·99; I^2 = 0 %; P-heterogeneity = 0·79) when comparing extreme categories (online Supplementary Fig. 2). In the dose–response analysis, an increase in whole milk intake by 100 g/d was inversely

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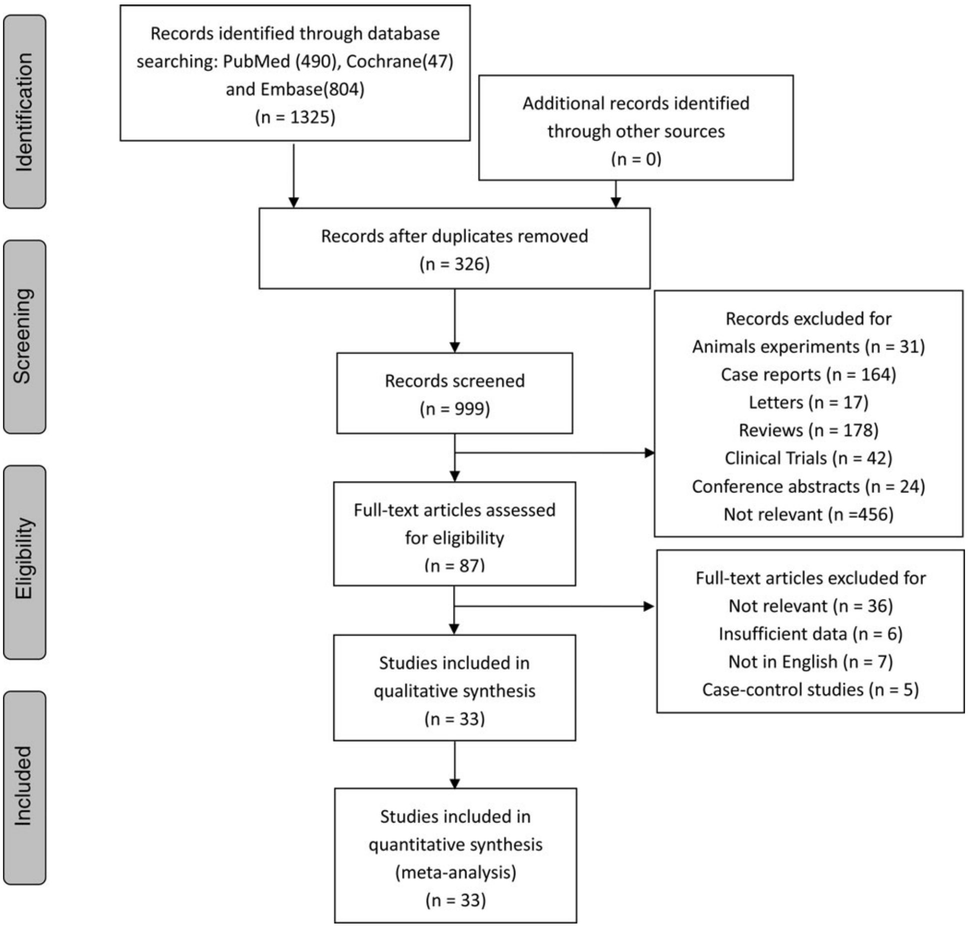

Fig. 1. Flow chart showing the systematic literature search and review.

associated with the risk of prostate cancer (RR: 0·97; 95 % CI 0·96, 0·99). There was evidence of a nonlinear association between whole milk intake and prostate cancer risk (*P*-nonlinearity = 0·04; *n* 7). The risk of prostate cancer decreased by 3 % with increasing the intake of whole milk ≤700 g/d (Fig. 4(c)).

Skim/low-fat milk

Four studies[19,32,54,56] with 12 534 prostate cancer cases were included in the meta-analysis comparing extreme intake categories (range of intake: 0–697 g/d). Comparing categories of highest and lowest intake of skim/low-fat milk, we observed no association with the risk of prostate cancer (RR: 1·10; 95 % CI 0·96, 1·26; $I^2 = 79$ %; *P*-heterogeneity < 0·01) (online Supplementary Fig. 3). In the dose–response analysis, an increase in skim/low-fat milk intake by 80 g/d was associated with the risk of prostate cancer (RR: 1·02; 95 % CI 1·00, 1·04). The results were insignificant when skim/low-fat milk intake was over 100 g/d. No evidence of a nonlinear dose–response association between skim/low-fat milk and the risk of prostate cancer was detected (*P*-nonlinearity = 0·20; *n* 4). The risk of prostate cancer increased by 2 % with increasing the intake of skim/low-fat milk ≤80 g/d. No additional risk increasing association is apparent above this value (Fig. 4(d)).

Cheese

Fifteen studies[20,21,28,33,37,39,40,45,46,48,49,51,52,54,56] with 33 236 prostate cancer cases were included in the meta-analysis comparing extreme intake categories (range of intake: 0–140 g/d). No significant association was observed between the prostate cancer risk and cheese intake (RR: 1·03; 95 % CI 0·99, 1·08; $I^2 = 0$ %; *P*-heterogeneity = 0·49) (online Supplementary Fig. 4). An increase in cheese intake by 40 g/d was associated with the risk of prostate cancer (RR: 1·01; 95 % CI 1·00, 1·03). No evidence of a nonlinear dose–response association between cheese and the risk of prostate cancer was found (*P*-nonlinearity = 0·47; *n* 15). The risk of prostate cancer increased by 9 % with increasing the intake of cheese ≤ 140 g/d (Fig. 4(e)).

Butter

Five studies[21,22,28,39,46] with 2943 prostate cancer cases were included in the highest compared with the lowest intake category meta-analysis (range of intake: 0–67 g/d). A positive association between the prostate cancer risk and butter intake was observed (RR: 1·08; 95 % CI 1·03, 1·12; $I^2 = 0$ %; *P*-heterogeneity = 0·42) (online Supplementary Fig. 5). An increase in butter intake by 50 g/d was associated with the risk of prostate cancer (RR: 1·03; 95 % CI 1·01, 1·05). There was evidence of a nonlinear dose–response association between butter and the risk of

Table 1. Characteristics of studies included in this meta-analysis
(Risk ratios and 95 % confidence intervals)

Study	Year	Country	Cohort name	No. of cases	Years of follow-up	Collection times	PC stage	Dairy type	Quantity	RR	95 % CI	Adjustment for confounders	NOS
Severson *et al.*	1989	USA	The HHP cohort: men of Japanese ancestry	174	22	1	Total PC	Butter Cheese Ice cream Milk	≥5 *v.* ≤1 times/ week ≥5 *v.* ≤1 times/ week ≥5 *v.* ≤1 times/ week ≥5 *v.* ≤1 times/ week	1·47 1·47 1·31 1·00	0·97, 2·25 0·97, 2·25 0·84, 2·03 0·73, 1·38	Age	6
Mills *et al.*	1989	USA	The Seventh-day Adventist men cohort	180	6	5	Total PC	Whole milk	≥daily *v.* Never	0·80	0·54, 1·19	Age	6
Thompson *et al.*	1989	USA	Rancho Bernardo Cohort	100	14	1	Total PC	Whole milk	/	0·90	0·70, 1·10	Age	6
Hsing *et al.*	1990	USA	The Lutheran Brotherhood Cohort	149	20	1	Fatal PC	Total dairy	86–189 *v.* <26 (times/month)	1·00	0·60, 1·70	Age, tobacco use	6
Veierød *et al.*	1997	Norway	/	72	12·4	2	Total PC	Skim milk Whole Milk	/	2·20 1·20	1·30, 3·70 0·60, 2·20	Age	7
Marchand *et al.*	1994	USA	The Hawaii Cohort	198	/	1	Total PC	Milk	1–2 *v.* 0 glasses/d	1·40	1·00, 2·10	Age, ethnicity, income by proportional hazards regression	8
Schuurman *et al.*	1999	Netherlands	The NLCS	642	6·3	3	Total PC	Cheese Milk	43 *v.* 2 g/d 566 *v.* 74 g/d	1·21 1·12	0·87, 1·70 0·81, 1·56	Age, family history of prostate cancer, socio-economic status, consumption of total fresh meat, poultry	8
Chan *et al.*	2000	Finland	The ATBC Study	184	8	1	Total PC	Total dairy	1119 *v.* 275 g/d	1·10	0·70, 1·70	Education, quintiles of age, BMI, energy, number of years as a smoker	8
Chan *et al.*	2001	USA	The Physicians' Health Study	1012	11	14	Total PC	Total dairy	>2·50 *v.* 0–0·50 servings/d	1·27	0·97, 1·66	Baseline measures of age in 12, 3 years categories, smoking, vigorous exercise, BMI, randomised treatment assignment in the original trial, quintiles of the food score	7
Michaud *et al.*	2001	USA	The Health Professional Follow-Up Study	2146	10	3	Total PC	Total dairy	>69 *v.* <19 g/d	1·07	0·88, 1·30	Age, energy content, Ca, smoking, tomato sauce, vigorous exercise, saturated fat, α-linolenic fat	9
Berndt *et al.*	2002	USA	The BLSA Cohort	162	/	1	Total PC	Cheese Milk Yogurt	4·30 *v.* 1·01 median daily serving 2·99 *v.* 0·26 median daily serving 4·30 *v.* 1·01 median daily serving	1·23 1·17 1·23	0·57, 2·79 0·58, 2·47 0·57, 2·79	Age, energy	7

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Table 1. (*Continued*)

Study	Year	Country	Cohort name	No. of cases	Years of follow-up	Collection times	PC stage	Dairy type	Quantity	RR	95 % CI	Adjustment for confounders	NOS
Rodriguez *et al.*	2003	USA	CPS-II Nutrition Cohort	3811	6	2	Total PC Advanced PC	Total dairy Total dairy	4 + servings/d *v.* < 3 servings/week 4 + servings/d. < 3 servings/week	1·10 0·90	0·90, 1·30 0·50, 1·40	Age at entry, race, family history of prostate cancer, total energy, total fat intake, education	8
Allen *et al.*	2004	Japan	Life Span Study cohort	196	17	3	Total PC	Butter Cheese Milk	Almost daily *v.* < 2 times/week Almost daily *v.* < 2 times/week Almost daily *v.* < 2 times/week	0·84 0·84 0·87	0·52, 1·37 0·52, 1·370·6-2, 1·21	Age, calendar period, city of residence, radiation dose, education level	9
Tseng *et al.*	2005	USA	The first National Health and Nutrition Examination Survey (NHANES I) Epidemiologic Follow-up Study (NHEFS)	131	6	4	Total PC	Total dairy Cheese Cream Ice cream Whole milk Yogurt Milk	21 *v.* 5 median servings/week 4 *v.* 0·25 median servings/week 0·5 *v.* 0 median servings/week 3 *v.* 0·1 median servings/week 7 *v.* 0 median servings/week 0·25 *v.* 0 median servings/week 14 *v.* 0·5 median servings/week	2·20 1·10 0·90 1·00 0·80 1·00 1·80	1·20, 3·90 0·60, 1·90 0·60, 1·30 0·70, 1·50 0·50, 1·30 0·60, 1·90 1·10, 2·90	Age, race, energy intake, design variables, US region, rural, urban, suburban residence, education, recreational sun exposure, recreational, usual level of physical activity, smoking status, current alcohol intake	8
Giovannucci *et al.*	2006	USA	The Health Professionals Follow-up Study	3544	16	4	Total PC Advanced PC	Total dairy Total dairy	3·72 *v.* 0·50 median servings/d 3·72 *v.* 0·50 median servings/d	1·05 1·08	0·91, 1·21 0·75, 1·55	Age, time period, BMI at age 21, vigorous physical activity, height, cigarette pack-years in the previous 10 years, family history of prostate cancer, history of diabetes mellitus, race, and intake of total energy content, red meat, fish, ALA, Zn supplements, tomato sauce	7
Koh *et al.*	2006	USA	The Harvard Alumni Health Study	815	10	1	Total PC Fatal PC	Total dairy Total dairy	≥3·25 *v.* < 1·25 servings/d ≥3·25 *v.* < 1·25 servings/d	1·11 1·12	0·85, 1.46 0·51, 2·47	Age, smoking, BMI, physical activity, intakes of alcohol, red meat, vegetables, total energetic intake and paternal history of prostate cancer	6
Tande *et al.*	2006	USA	The ARIC Study	383	12·1	1	Total PC	Milk	≥1·00 *v.* <0·07 servings/d	1·46	1·06, 2·01	Age, race	7

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Table 1. (*Continued*)

Study	Year	Country	Cohort name	No. of cases	Years of follow-up	Collection times	PC stage	Dairy type	Quantity	RR	95 % CI	Adjustment for confounders	NOS
Kesse *et al.*	2006	France	SU.VI.MAX study	69	7·7	5	Total PC	Total dairy Cheese Milk Yogurt	>396 *v.* <160 g/d >71 *v.* <25 g/d >253 *v.* <25 g/d >100 *v.* 0 g/d	1·33 0·65 0·83 1·46	0·52, 3·45 0·29, 1·44 0·39, 1·77 0·68, 3·14	Occupation, group of treatment, smoking status, overall physical activity, energy from fat, energy from others sources, ethanol intake, BMI, family history of prostate cancer in first-degree relative, dietary energy-adjusted Ca intake (RR2)	8
Song-Yi Park *et al.*	2007	USA	Multiethnic Cohort Study	4404	8	1	Total PC Non-advanced PC Advanced PC	Total dairy Cheese Milk Yogurt Whole milk Total dairy Total dairy	>332 *v.* <49 g/d >14 *v.* 0 g/d >256 *v.* <17 g/d >40 *v.* 0 g/d >163 *v.* 0 g/d >332 *v.* <49 g/d >332 *v.* <49 g/d	1·03 1·01 1·07 0·96 0·88 1·14 0·97	0·92, 1·16 0·91, 1·12 0·95, 1·19 0·84, 1·09 0·77, 1·00 0·97, 1·34 0·72, 1·31	Strata variables time since cohort entry, ethnicity, family history of prostate cancer, education, BMI, smoking status, energy intake as a covariate	7
Rohrmann *et al.*	2007	USA	CLUE II study	199	13	1	Total PC Non-advanced PC Advanced PC	Total dairy Cheese Milk Total dairy Total dairy	1·9 + *v.* 0·9 servings/d 5 + *v.* ≤1 time/week 5 + *v.* ≤1 time/week 1·9 + *v.* 0·9 servings/d 1·9 + *v.* 0·9 servings/d	1·08 1·43 1·26 1·31 1·28	0·78, 1·54 1·01, 2·03 0·91, 1·74 0·71, 2·41 0·63, 2·59	Age, energy intake, consumption of tomato products, BMI at age 21, intake of saturated fat	7
Van der Pols *et al.*	2007	UK	The Boyd Orr Cohort	770	65	1	Total PC	Total dairy Milk	471 *v.* 89 g/d ≥1·2 cups (≥282 ml) *v.* <0·5 cup (<118 ml)	0·55 0·41	0·21, 1·42 0·16, 1·05	Fruit, vegetable, fat intakes, weight, height, district, season of the survey, socio-economic status, per capita food expenditure of the household	8
Yikyung Park *et al.*	2007	USA	National Institutes of Health (NIH)-AARP Diet and Health Study	10 180	6	1	Total PC Non-advanced PC Advanced PC Fatal PC	Total dairy Cheese Skim milk Yogurt Whole milk Total dairy Total dairy Total dairy	≥3 *v.* <0·5 servings/d ≥2 *v.* <0·1 servings/d ≥2 *v.* 0 servings/d 0·5–<1 *v.* 0 servings/d ≥2 *v.* 0 servings/d ≥3 *v.* <0·5 servings/d ≥3 *v.* <0·5 servings/d ≥3 *v.* <0·5 servings/d	0·96 1·08 1·01 1·01 0·91 0·98 0·82 0·99	0·87, 1·06 0·96, 1·22 0·93, 1·10 0·89, 1·15 0·76, 1·09 0·88, 1·10 0·63, 1·08 0·47, 2·09	Age, race/ethnicity, education, marital status, BMI, vigorous physical activity, smoking, alcohol consumption, history of diabetes, family history of prostate cancer, screening for prostate cancer by use of PSA, intakes of tomatoes, red meat, fish, vitamin E, ALA, total energy, total Ca, total vitamin D	9

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Table 1. (*Continued*)

Study	Year	Country	Cohort name	No. of cases	Years of follow-up	Collection times	PC stage	Dairy type	Quantity	RR	95 % CI	Adjustment for confounders	NOS
Neuhouser *et al.*	2007	USA	Carotene and Retinol Efficacy Trial (CARET)	890	11	1	Total PC	Total dairy	≥2·2 *v.* <0·9 servings/d	0·82	0·66, 1·02	Age, energy intake, BMI, smoking, family history of prostate cancer	8
Mitrou *et al.*	2007	Finland	The ATBC study cohort	1267	17	1	Total PC	Total diary	1220·2 *v.* 380·9 g/d	0·87	0·66, 1·14	Age, trial intervention group, physical activity at work and at leisure, history of type II diabetes, family history of prostate cancer, height, BMI, smoking inhalation, total number of cigarettes/d, marital status, education, urban residence, total energy intake, dietary Ca	8
								Butter	71·7 *v.* 5·1 g/d	1·04	0·87, 1·25		
								Cheese	54·6 *v.* 3·0 g/d	1·04	0·86, 1·25		
								Cream	47·7 *v.* 1·2 g/d	1·11	0·93, 1·33		
								Ice cream	9·3 *v.* 0 g/d	0·90	0·75, 1·08		
								Milk	993·5 *v.* 152·6 g/d	0·86	0·70, 1·07		
Ahn *et al.*	2007	USA	The PLCO Cancer Screening Trial	1910	8·9	1	Total PC	Total dairy	≥2·75 *v.* ≤0·98 servings/d	1·06	0·88, 1·30	Age, race, study centre, family history of prostate cancer, BMI, smoking status, physical activity, history of diabetes, red meat intake, total energy intake, education, number of screening examinations	7
Kurahashi *et al.*	2008	Japan	The Japan Public Health Center–Based Prospective Study	329	7·5	1	Total PC	Total diary	339·8 *v.* 12·8 g/d	1·63	1·14, 2·32	Age, area, smoking status, drinking frequency, marital status, and intake of green tea, genistein	7
							Non-advanced PC	Cheese	6·2 *v.* 1·9 g/d	1·32	0·93, 1·89		
								Milk	290·5 *v.* 2·3 g/d	1·53	1·07, 2·19		
								Yogurt	31·5 *v.* 1·9 g/d	1·52	1·10, 2·12		
							Advanced PC	Total diary	339·8 *v.* 12·8 g/d	1·69	1·10, 2·59		
								Total diary	339·8 *v.* 12·8 g/d	1·41	0·73, 2·73		
Allen *et al.*	2008	Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden and the UK	The European Prospective Investigation into Cancer and Nutrition	2727	8·7	1	Total PC	Cheese	57 *v.* 15 g/d	1·04	0·90, 1·20	Education, marital status, height, weight, energy intake	6
								Milk	466 *v.* 34 g/d	1·01	0·89, 1·16		
								Yogurt	135 *v.* 10 g/d	1·29	1·14, 1·45		
Park *et al.*	2009	USA	The NIH-AARP Diet and Health Study	53 570	7	1	Total PC	Total dairy	1·4 *v.* 0·2 serving/4184 kJ/d	1·06	1·01, 1·12	Age, race ethnicity, education, marital status, BMI, FH-cancer, diabetes, physical activity, ALA, alcohol, red meat, total energy, smoking, PSA test, tomatoes, Se	8

Table 1. (*Continued*)

Study	Year	Country	Cohort name	No. of cases	Years of follow-up	Collection times	PC stage	Dairy type	Quantity	RR	95 % CI	Adjustment for confounders	NOS
Song *et al.*	2012	USA	The PHS	2806	28	1	Total PC	Total dairy Cheese Ice cream Skim milk Whole milk	>2·5 *v.* ≤0·5 servings/d ≥1 serving/d *v.* ≤1 serving/week ≥1 serving/d *v.* ≤1 serving/week ≥1 serving/d *v.* ≤1 serving/week ≥1 serving/d *v.* ≤1 serving/week	1·12 1·05 1·03 1·19 0·95	0·93, 1·35 0·85, 1·30 0·80, 1·32 1·06, 1·33 0·81, 1·10	Age, cigarette smoking, vigorous exercise, alcohol intake, race, BMI, baseline diabetes status, red meat consumption, total energy intake from recorded food items, assignment in the original aspirin trial and assignment in the original β-carotene trial	6
Papadimitriou *et al.*	2019	UK	The European Prospective Investigation into Cancer and Nutrition (EPIC)	5916	14	1	Total PC	Butter	/	1·07	1·02, 1·11	Total energy intake, smoking status, BMI, physical activity, diabetes, education	6
Preble *et al.*	2019	USA	The PLCO cohort	4134	11·2	1	Total PC Non-advanced PC Advanced PC	Total dairy Skim milk Milk Whole milk Total dairy Total dairy	>194·7 *v.* <47·2 g/4184 kJ >89·5 *v.* 0 g/4184 kJ >163·9 *v.* <21·8 g/4184 kJ >37·0 *v.* 0 g/4184 kJ >194·7 *v.* <47·2 g/4184 kJ >194·7 *v.* <47·2 g/4184 kJ	1·05 1·00 1·06 1·00 1·09 1·02	0·96, 1·15 0·92, 1·09 0·97, 1·15 0·88, 1·13 0·96, 1·23 0·90, 1·16	Age, race, PLCO study centre, PLCO trial arm, frequency of prostate cancer screening during the follow-up period, maximum PSA level during follow-up period, family history of any cancer	8
Nilsson *et al.*	2019	Sweden	Northern Sweden Health and Disease Study cohorts (NSHDS)	12 552	11·2	1	Total PC	Butter Cheese	3·5 *v.* 0·030 servings/d 2·4 *v.* 0·18 servings/d	1·13 1·03	0·99, 1·28 0·82, 1·29	Age, screening year, dairy product category, BMI, civil status, education level, physical activity in leisure time, smoking status, recruitment cohort, quintiles of fruit and vegetables, alcohol, energy intake	7
Lan *et al.*	2020	USA	The NIH-AARP Diet and Health Study	17 729	14	1	Total PC Advanced PC Fatal PC	Total dairy Cheese Ice cream Milk Total dairy Total dairy	Per time/d *v.* ≤ 4 times/week Per time/d *v.* ≤ 3 times/month Per time/d *v.* ≤ 3 times/month Per time/d *v.* ≤ 2 times/week Per time/d *v.* ≤ 4 times/week	1·01 0·98 0·92 1·01 0·98 0·91	0·99, 1·03 0·91, 1·06 0·84, 1·00 0·99, 1·03 0·93, 1·03 0·83, 1·00	Age, adolescent energy intake, race, family history of prostate cancer, education, marital status, cigarette smoking history, adult alcohol intake, adult waist circumference, BMI at ages 18, 35, 50, baseline, adolescent, adult physical activity, PSA,	8

Table 1. (*Continued*)

Study	Year	Country	Cohort name	No. of cases	Years of follow-up	Collection times	PC stage	Dairy type	Quantity	RR	95 % CI	Adjustment for confounders	NOS
									Per time/d *v.* ≤ 4 times/week			digital rectal examination screening history, diabetes history, father's occupation, attained height, adult intake of whole milk, cheese, ice cream, total high-fat dairy products, Ca, adolescent intake of grains, vegetables, fruits, potatoes, red meat, sweets	

PC, prostate cancer; RR, relative risk; NOS, Newcastle–Ottawa scale; ALA, α-linolenic acid; PSA, prostate-specific antigen.

prostate cancer (P-nonlinearity = 0·01; n 4). The risk of prostate cancer increased by 3 % with increasing the intake of cheese ≤ 50 g/d (Fig. 4(f)).

Yogurt

Seven studies[37,40,45,48,51,52,56] with 8802 incident cases were included in the meta-analysis comparing highest and lowest intake of yogurt (range of intake: 0–802 g/d). No significant association was detected with the risk of prostate cancer (RR: 1·14; 95 % CI 0·98, 1·32; I^2 = 65 %; P-heterogeneity < 0·01) (online Supplementary Fig. 6). Similarly, in the dose–response analysis, an increase in yogurt intake by 100 g/d was not associated with the risk of prostate cancer (RR: 1·03; 95 % CI 0·97, 1·09). No evidence of a nonlinear dose–response association between yogurt and the risk of prostate cancer was observed (P-nonlinearity = 0·40; n 5) (Fig. 4(g)).

Ice cream

Five studies[20,28,40,46,54] with 5268 incident cases were included in the meta-analysis comparing highest and lowest intake of ice cream (range of intake: 0–173 g/d). The association was insignificant between the ice cream intake and the risk of prostate cancer (RR: 0·94; 95 % CI 0·87, 1·01; I^2 = 0 %; P-heterogeneity = 0·52) (online Supplementary Fig. 7). In the dose–response analysis, an increase in ice cream intake by 100 g/d was not associated with the risk of prostate cancer (RR: 0·99; 95 % CI 0·97, 1·01). There was no evidence of a nonlinear dose–response association between ice cream and the risk of prostate cancer (P-nonlinearity = 0·75; n 4) (Fig. 4(h)).

Cream

Two studies[40,46] with 1398 incident cases were included in the meta-analysis. Cream intake was not associated significantly with prostate cancer (RR: 1·07; 95 % CI 0·91, 1·26; I^2 = 0 %; P-heterogeneity = 0·33) (online Supplementary Fig. 8). More studies are needed to evaluate the potential relationship between cream consumption and prostate cancer.

Subgroup analyses

The results of the subgroup analyses are shown in Table 2. For the subgroups stratified by prostate cancer type, follow-up years, treatment era, collection times, adjustment for confounders and geographic location, we only included studies that provided total dairy intake data. As only a few studies provided unadjusted RR, all of the results were summarised using adjusted RR. In the subgroup analysis stratified by years of follow-up, we included twenty-five studies that provided the data of total dairy intake. The pooled RR were 1·03 (95 % CI 0·97, 1·09) in group with a follow-up duration more than 10 years and 1·06 (95 % CI 0·99, 1·14) in group with a follow-up duration less than 10 years. In the subgroup analysis stratified by prostate cancer type, the pooled RR were 0·98 (95 % CI 0·94, 1·03) in the advanced group, 1·10 (95 % CI 0·98, 1·24) in the non-advanced group and 0·92 (95 % CI 0·84, 1·00) in the fatal group (Fig. 5). Based on geographic location, the association was not statistically significant in Europe (RR: 0·95; 95 % CI 0·77, 1·16), whereas it remained

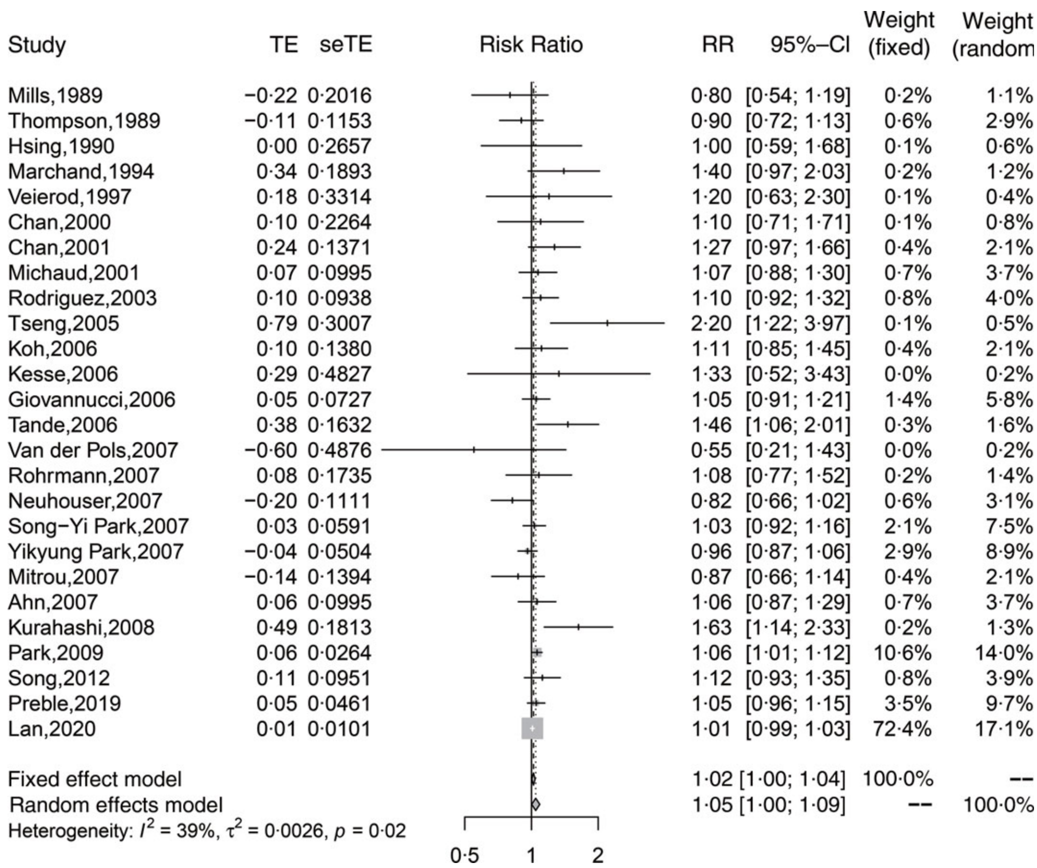

Fig. 2. Forest plot for total dairy products consumption associated with risk of prostate cancer. RR, relative risk.

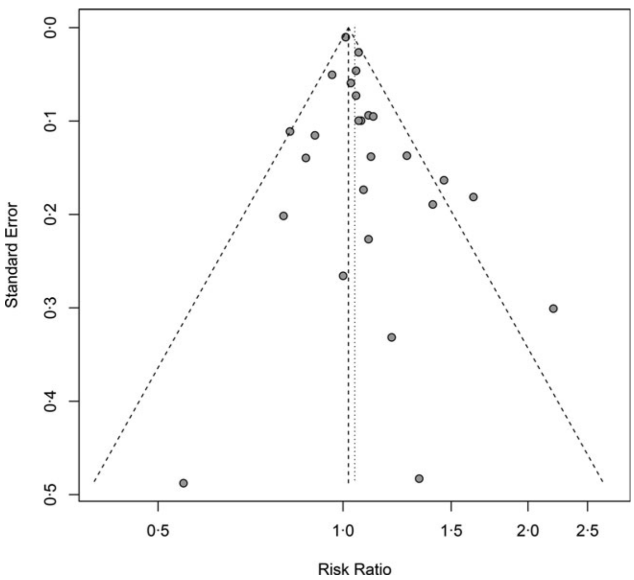

Fig. 3. Funnel plot for total dairy products consumption associated with risk of prostate cancer. RR, relative risk.

significant in the USA (RR: 1·04; 95 % CI 1·00, 1·08) and Asia (RR: 1·63; 95 % CI 1·14, 2·32). The impact of measurement times on the final results was investigated by stratifying analyses according to collection times of dietary information, and significant association only limited in one-time measurement (RR: 1·04; 95 % CI 1·00, 1·08). Men were categorised into two groups stratified by the treatment era: the pre-PSA screening era (before 1991) and the PSA screening era (after 1991).The eras were defined because PSA was initially reported as a first-line screening test for prostate cancer in 1991 and was not routinely used as an aid for early detection before that time[57]. Three studies conducted in pre-PSA era showed insignificant results (RR: 0·89; 95 % CI 0·74, 1·07) while the results remained significant in the studies conducted in PSA era (RR: 1·05; 95 % CI 1·01, 1·10). In the analyses stratified by adjustment for different confounders, the significant results did not persist in the studies that adjusted for Ca and vitamin D, energy intake, history of diabetes and PSA test.

Discussion

In our study, we pooled data from thirty-three cohort studies to update the evidence of the relationship between the consumption of dairy products and the risk of prostate cancer. Our study showed an increased risk of prostate cancer with high intakes of total dairy products, milk, cheese and butter. An inverse association was found with whole milk. No relationship was observed between skim/low-fat milk, yogurt, ice cream, cream and prostate cancer risk. In the dose–response analysis, a positive association was present for total dairy, total milk, skim/low-fat milk,

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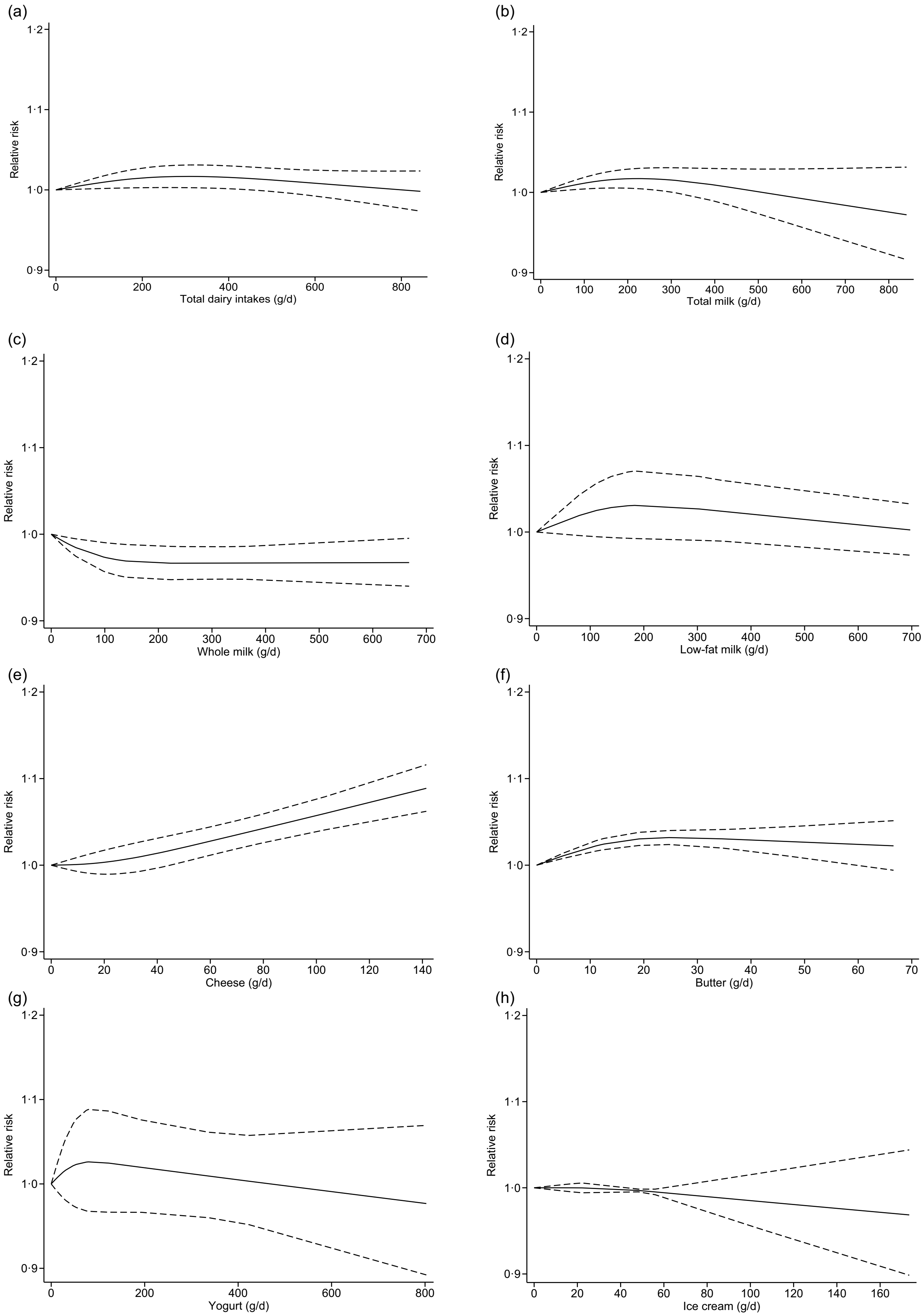

Fig. 4. Nonlinear dose–response relation between daily intakes of total dairy products (a) (*P*-nonlinearity = 0·03; *n* 20 studies), total milk (b) (*P*-nonlinearity < 0·01; *n* 16 studies), whole milk (c) (*P*-nonlinearity = 0·04; *n* 7 studies), skim/low-fat milk (d) (*P*-nonlinearity = 0·20; *n* 4 studies), cheese (e) (*P*-nonlinearity = 0·47; *n* 15 studies), butter (f) (*P*-nonlinearity = 0·01; *n* 4 studies), yogurt (g) (*P*-nonlinearity = 0·40; *n* 5 studies) and ice cream (h) (*P*-nonlinearity = 0·75; *n* 4 studies) and the risk of prostate cancer.

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Table 2. Results of subgroup analyses
(Risk ratios and 95 % confidence intervals)

	Subgroup	Number of studies	Heterogeneity I^2 (%)	Heterogeneity *P*	RR	95 % CI
Dairy type	Total milk	17	46	0·02	1·07	1·00, 1·14
	Whole milk	7	0	0·79	0·93	0·87, 0·99
	Skim/low-fat milk	4	79	<0·01	1·10	0·96, 1·26
	Cheese	15	0	0·49	1·03	0·99, 1·08
	Butter	5	0	0·42	1·08	1·03, 1·12
	Yogurt	7	65	<0·01	1·14	0·98, 1·32
	Ice cream	5	0	0·52	0·94	0·87,1·01
	Cream	2	0	0·33	1·07	0·91, 1·26
Follow-up duration	≤10 years	12	39	0·08	1·06	0·99, 1·14
	>10 years	13	32	0·13	1·03	0·97, 1·09
Prostate cancer stage	Non-advanced	5	49	0·10	1·10	0·98, 1·24
	Advanced	8	0	0·76	0·98	0·94, 1·03
	Fatal	4	0	0·94	0·92	0·84, 1·00
Collection times	Multiple times	9	48	0·05	1·07	0·94, 1·21
	One times	17	36	0·07	1·04	1·00, 1·08
Geographic location	USA	20	38	0·04	1·04	1·00, 1·08
	Europe	5	0	0·55	0·95	0·77, 1·16
	Asia	1	–	–	1·63	1·14, 2·32
Treatment era	Pre-PSA era	3	0	0·79	0·89	0·74, 1·07
	PSA era	23	43	0·02	1·05	1·01, 1·10
Adjustment for confounders						
Alcohol intake	Adjusted	7	68	<0·01	1·06	0·99, 1·13
	Unadjusted	19	15	0·27	1·04	0·98, 1·10
BMI	Adjusted	14	0	0·52	1·02	1·00, 1·04
	Unadjusted	12	60	<0·01	1·10	0·98, 1·25
Ca and vitamin D	Adjusted	4	0	0·48	1·01	0·99, 1·03
	Unadjusted	22	34	0·06	1·07	1·02, 1·14
Energy intake	Adjusted	14	30	0·14	1·03	0·99, 1·07
	Unadjusted	12	43	0·06	1·12	1·00, 1·26
History of diabetes	Adjusted	5	0	0·59	1·01	0·99, 1·03
	Unadjusted	21	43	0·02	1·06	1·00, 1·13
Physical activity	Adjusted	12	36	0·11	1·04	0·99, 1·08
	Unadjusted	14	44	0·04	1·06	0·96, 1·16
PSA test	Adjusted	4	36	0·19	1·02	0·99, 1·06
	Unadjusted	22	38	0·04	1·08	1·00, 1·16
Smoking status	Adjusted	17	42	0·03	1·04	0·99, 1·09
	Unadjusted	9	34	0·15	1·07	0·96, 1·19

RR, risk ratio; PSA, prostate-specific antigen.

cheese and butter. On the other side, whole milk was associated with a lower risk of prostate cancer. We observed some evidence of nonlinearity between the intakes of total dairy, total milk, whole milk and butter with the risk of prostate cancer.

Several meta-analysis articles have explored this topic. Gao *et al.*[14] in 2005 included ten prospective studies and found men with the highest intake of dairy products were more likely to develop prostate cancer than men with the lowest intake, with pooled RR 1·11 (95 % CI 1·00, 1·22). In 2008, Huncharek *et al.*[16] pooled eleven cohort studies and found no evidence of an association between dairy or milk intake and risk of prostate cancer, with RR for the highest intake category *v.* the lowest intake category 1·06 (95 % CI 0·92, 1·22) and 1·06 (95 % CI 0·91, 1·23), respectively. In 2015, Aune *et al.*[17] included thirty-two cohort studies in the analysis of dairy product and Ca intake and prostate cancer risk. Comparing the highest with the lowest intakes, the summary RR for total dairy products consumption and prostate cancer risk was 1·09 (95 % CI 1·02, 1·17). In the dose–response analysis, a significant 7 % increase in prostate cancer risk for every 400 g of total dairy products consumed/d was observed. Compared with the previous study, we included a large number of studies with thirty-three in total and carried out more thorough analyses. In addition to the previous findings, we found that butter was also associated with higher prostate cancer risk. In 2018, the World Cancer Research Fund/American Institute for Cancer Research have reported that there is not sufficient evidence to recommend reducing milk and dairy consumption to reduce the risk of cancer[18]. Although we found that higher dairy consumption increased prostate cancer risk, the RR for highest compared with lowest intakes was reduced from 9 % to 5 %, which is closer to the actual effect size. In the dose–response analysis, the result became insignificant when total dairy intake was over 500 g/d. This reduction indicates that with more evidence available, the association between dairy product consumption and prostate cancer risk is smaller and better defined.

Several mechanisms may help explain the relationship between dairy product intakes and the increased risk of prostate cancer. Many observational and experimental studies have reported that higher intakes of milk and dairy products are

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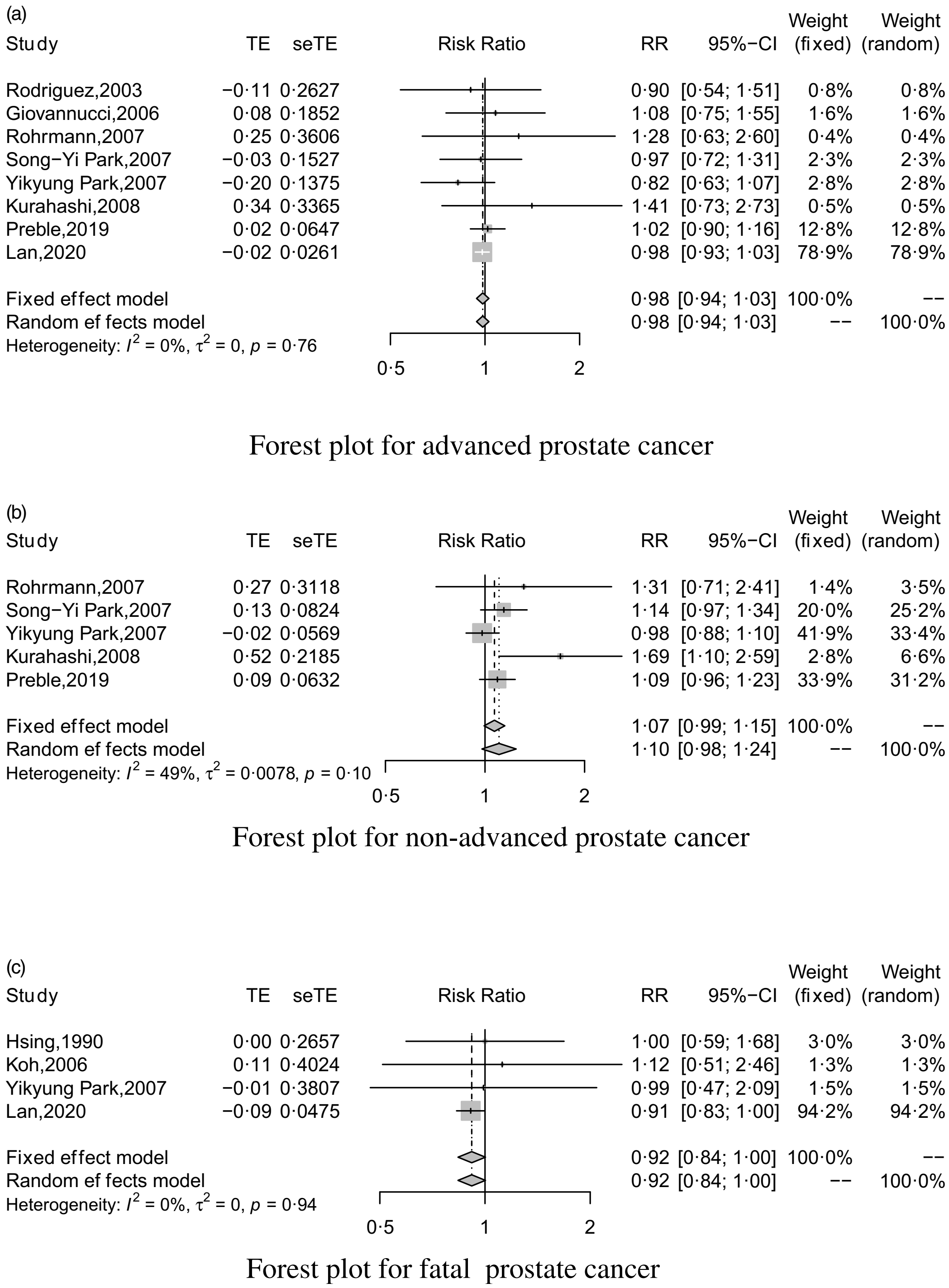

Fig. 5. Forest plot for total dairy products consumption associated with risk of prostate cancer stratified by subtypes. (a) Forest plot for total dairy products consumption associated with risk of advanced prostate cancer. (b) Forest plot for total dairy products consumption associated with risk of non-advanced prostate cancer. (c) Forest plot for total dairy products consumption associated with risk of fatal prostate cancer. RR, relative risk.

associated with increased circulating concentrations of insulin-like growth factor 1 (IGF-1)[58-60]. Qin *et al.*[61] found that the milk intervention significantly increased 13·8 ng/ml of circulating IGF-1 levels by conducting a meta-analysis of cross-sectional studies and randomised controlled trials. In the past years, several research articles have recognised that the IGF system plays an important role in prostate cancer biology[62]. The IGF system regulates many important cellular processes that are crucial for normal prostate proliferation, differentiation and cellular metabolism[63]. Additionally, IGF-1 also promotes proliferation and inhibits apoptosis *in vitro* in prostate cancer cells[64]. Several prospective studies have seen the correlation between IGF-1 and increased prostate cancer risk[65,66]. Results of a meta-analysis estimated that men with the highest IGF-1 levels might have an approximately 70 % increase in risk for prostate cancer[67].

Our study found that the association between prostate cancer and dairy intakes differed by dairy food type. The potential mechanism was that different dairy products were associated with different concentrations of insulin-related/IGF-signalling and inflammatory biomarkers. A number of studies have reported associations between circulating inflammatory biomarkers and prostate cancer risk[68-70]. Shi *et al.*[71] assessed the associations between total dairy and individual dairy foods with circulating concentrations of insulin-related/IGF-signalling and inflammation-related biomarkers. They found that higher intakes of low-fat dairy and yogurt were associated with lower IGF-1 concentrations, while higher intakes of milk and butter were associated with higher IGF-1 concentrations. Similarly, our study presented that skim/low-fat milk and yogurt were not associated with prostate cancer risk, while total milk and butter were associated with increased prostate cancer risk. The study also showed that higher intake of full-fat dairy including whole milk was associated with lower concentrations of inflammatory biomarkers. This might explain the inverse relationship between whole milk intake and prostate cancer that we found.

A recent study[72] determined the association between hyperinsulinaemic dietary patterns, which included full-fat dairy as favourable component, and prostate cancer incidence and mortality. They found that in the multivariable-adjusted analyses, the hyperinsulinaemic diet was associated with advanced and fatal prostate cancer. Hyperinsulinaemia may promote tumour growth directly through insulin receptors or regulation of IGF and their binding proteins (IGFBP), which are involved in cell survival and proliferation. However, in our subgroup analysis stratified by prostate cancer type, we did not find positive association between dairy intakes and advanced or fatal prostate cancer. This finding needs additional study because only four studies were included in the subgroup of fatal prostate cancer.

Oestrogen may be another mechanism through which dairy intake may contribute to the aetiology of prostate cancer[73]. Sixty to seventy percentage of animal-derived oestrogens in the human diet come from milk and dairy products[74]. Moreover, modern genetically improved dairy cows continue to lactate throughout almost the entire pregnancy, leading to large amounts of oestrogens contained in commercial cow's milk[75]. An ample body of evidence suggests that oestrogens may play a critical role in causing prostate cancer[76-78]. As estradiol-17β has been classified as a carcinogen by the International Agency for Research on Cancer, oestrogen contained in dairy products should be considered as a potential risk factor for prostate cancer[79].

Finally, the intakes of dairy products focused on Ca may be associated with an increased risk of prostate cancer. Dairy products are Ca-rich foods. The Health Professional Follow-Up Study analysed the diet of 47 885 men and looked closely at the participants' consumption of Ca. After a 24-year follow-up, 5861 cases of prostate cancer were identified and the result RR of 1·24 (95 % CI 1·02, 1·51) indicated that prostate cancer was associated with high Ca intake[80]. Some scientists suggested that higher Ca intake may down-regulate the circulating vitamin D concentration, which plays an important role in inhibiting cellular proliferation and neoplastic cell differentiation[81].

Our meta-analysis has three strengths. First, we included thirty-three studies in the main analyses and the ample number of articles allowed us to have adequate statistical power to detect significant relationships. Second, the studies included are all prospective cohorts, thus avoiding recall bias and reducing the risk of selection bias. Third, the robust error meta-regression method did not require the distribution of cases or person-years so more studies were available in the dose–response analysis.

We also acknowledge several potential limitations to the current study. First, the result may be confounded because dairy product intakes are associated with other risk factors such as PSA testing, energy intake, obesity, alcohol and smoking[82-85]. The association between total dairy consumption and prostate cancer became insignificant in the groups that adjusted for PSA test, Ca and vitamin D, history of diabetes and energy intake. Second, studies that adjusted for potential confounding were limited, thus having weaker statistical power. According to recent research studies, around 20–40 % of the prostate cancer cases in the USA and Europe could be due to overdiagnosis through extensive PSA testing[86]. In the four studies that adjusted for PSA testing[19,20,53,56], the association became insignificant. Therefore, the positive relationship between dairy product intakes and prostate cancer incidence might simply have reflected more cancers being detected. Nonetheless, for most of the dairy product types, studies that adjusted for PSA testing are very few, making it difficult to draw a conclusion. PSA testing is much more common in the USA than in Europe[87], so the significant result of USA studies might be impacted by this. As only one study conducted in Asia provided total dairy data, it was hard to draw the conclusion that results differed by geographical location. In addition, people with higher intakes of whole milk or more hyperinsulinaemic diet might have a lower PSA screening rate[72], thus confounding by PSA screening should be considered a potential bias. Finally, some subgroups were investigated in a limited number of studies. For example, the cream group only included two studies. The non-advanced group and fatal group also lacked abundant data, with merely five and four studies included respectively.

Conclusions

In conclusion, we showed an increased risk of prostate cancer with consumption of total dairy products, milk, cheese and butter but an inverse association for whole milk and no association with skim/low-fat milk, yogurt, ice cream and cream. Additional studies need to further explore the association between dairy product consumption and different subtypes of prostate cancer.

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Z. Z.: Conceptualisation, Methodology, Formal analysis, Investigation, Data interpretation, Writing – original draft,

Writing – review and editing ; D. W.: Methodology, Data interpretation; D. Z.: Methodology, Data interpretation and Data curation; S. G.: Formal analysis and Data curation; X. Z.: Data interpretation and Data curation; Y. Y.: Data interpretation and Data curation; Y. X.: Data interpretation and Data curation. All authors critically reviewed and approved the final manuscript.

There are no conflicts of interest.

Supplementary material

For supplementary material referred to in this article, please visit https://doi.org/10.1017/S0007114522002380

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