Original Article

Milk consumption is a risk factor for prostate cancer in Western countries: evidence from cohort studies

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We have previously found a positive association between milk consumption and prostate cancer risk using meta-analysis to analyze published case-control studies. In the present study, further meta-analysis was conducted to estimate the summary relative risk (RR) between the consumption of milk and dairy products and prostate cancer from cohort studies published between 1966- 2006. We found 18 relevant articles and 13 independent studies were available for our analysis. The summary RR was 1.13 (95% confidence interval = 1.02-1.24) when comparing the highest with the lowest quantile of consumption. The summary RRs by study stratification showed a positive association. A dose-response relationship was identified when combining the studies that partitioned the consumption by quintiles. We also evaluated the effects of some limitations, such as dairy classification, prostate cancer stages and publication bias, in the present study. These findings, together with the previous study, suggest that the consumption of milk and dairy products increases the risk of prostate cancer. This is biologically plausible since milk contains considerable amounts of fat, hormones, and calcium that are associated with prostate cancer risk.

Key Words: milk, dairy products, prostate cancer, meta-analysis, cohort study, oriental populations

INTRODUCTION

Prostate cancer is the most commonly diagnosed cancer and the second leading cause of cancer death in United States males.[1] The incidence and mortality are also increasing rapidly in China and other Asian countries, whose populations are generally at low risk.[2] Although the risk factors for prostate cancer have been researched for several decades, only age, ethnicity and family history of prostate cancer are well-established.[3] Thus, feasible measures for primary prevention of the disease remain limited.

Epidemiological research has implicated a "Western" lifestyle as a risk factor for prostate cancer.[4] Dietary factors are thought to be the most responsible for the change in incidence rates among migrants.[5-7] To find the foods that contribute to this risk, we collected cancer rates and food supply data from 42 countries and found that milk was the food most closely correlated with prostate cancer incidence (r = 0.711) and mortality (r = 0.766).[8] Since milk is an important staple in Western countries and is becoming popular in China where milk is not a traditional food, the health issue of milk consumption is worth investigating using other epidemiological methods and laboratory studies.

In general, case-control and cohort studies are more credible than our ecological study that evaluated consumption through "food disappearances" in different populations. However, the conclusion about a relationship between the consumption of milk and dairy products and prostate cancer is more contradictory in the case-control and cohort studies than in ecological studies.[8,9] One of the possible limitations in individual case-control studies or sometimes in cohort studies is the small number of cases and participants. Meta-analysis, a statistical method, is able to overcome some of the sample size limitations in the published data and provide the stronger or clearer conclusions.[10]

In our recent study, we combined all published case-control studies using meta-analysis and found the combined odds ratio (OR) between milk consumption and prostate cancer incidence to be 1.68 with a 95% confidence interval (CI) = 1.32-2.12.[9] Considering the different designs and the limitations of the software, the cohort study has not been included in the previous meta-analysis. In general, case-control studies can be susceptible to recall and selection biases that lead to spurious association. However, in a cohort study, diet is assessed in defined subjects before the onset of disease in those who become cases.

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Manuscript received 2 March 2006. Initial review completed 14 July 2006. Revision accepted 25 September 2006.

Since the cohort study is more effective than a case-control study, summary of all relevant cohort studies using a suitable method is more convincing. Of course, a well-designed cohort study with a large sample is more important than meta-analysis.

However, if the results of several cohort studies are still inconsistent, meta-analysis will provide a way to mitigate the inconsistency and to direct further research. We thus tried to perform a meta-analysis using published cohort studies to clarify the relationship between consumption of milk and dairy products and prostate cancer risk.

MATERIALS AND METHODS

We searched MEDLINE from January 1966 to July 2006 for all articles including "milk", "dairy", "cheese", "ice-cream" and "prostate cancer" as keywords in subject heading, title and abstract. The searches were limited to studies published in English. Because some studies that presented data on milk may not have included these specific terms in their abstracts, we carried out a broader search for all studies that looked at "diet" and "prostate cancer". Reference lists of the resulting articles were also searched for additional relevant literatures.

A study was included as a candidate if it met the following criteria: 1) it presented original data from a cohort study. A nested case-control study was treated as a cohort study for the analysis. 2) The primary outcome was clearly defined as prostate cancer. In this case that relative risk (RR) was calculated according to the stage of disease, the RR extracted for analysis is that covering the widest range of stages or representing the latest stage if separated stages were reported. 3) The exposure of interest included milk or dairy products. Butter is a fat rather than a product representative of the wider nutritional properties of milk. Thus, butter, as an independent item, is not included in this meta-analysis. To our knowledge, the dairy products examined by most researchers include whole milk, low-fat milk, cheese and so on. To avoid confusion, "dairy", "dairy products" and "milk and dairy (its) products" used in the original studies were termed as "dairy products" in the present analysis. Cheese or ice cream were not included in the analysis of "diary products" if they were presented individually. However, if they were observed as an independent item in more than three studies, a summary RR would be calculated. 4) RR with 95% CI was provided or raw data was available to calculate these parameters. In order to avoid giving double weight to some studies, the most recent article including the desired item was retained if these articles came from the same project or the samples were found to overlap.

Because of the different ranks and different dietary assessment methods, it is difficult to standardize all studies in a meta-analysis. In the present analysis, the RR and 95% CI extracted for this meta-analysis were compared for the highest and lowest quantiles of consumption and reflected the greatest degree of control for confounders. Two researchers performed data extraction independently. Differences in data extraction were resolved by discussion.

LnRR was weighted by the inverse of their variances to obtain a pooled measure of RR.

$$\ln(RR) = \Sigma[\omega i \times \ln(RRi)] \div \Sigma\omega i$$

$$\omega i = 1 \div \text{variance}(RRi)$$

The variances were calculated based on the reported confidence intervals.[11]

$$\text{variance}(RRi) = [\ln(RRu \div RRl) \div 3.92]^2$$

RRi is the estimate of the RR in the ith study. RRu is the upper confidence limit and RRl is the lower confidence limit of the 95% CI for that study.

A 95% CI was approximated by natural-logarithm transformation and expressed again by natural-antilogarithm transformation of the data.

$$95\%\ CI = EXP\{\ln(RR) \pm [1.96 \times SQRT(\Sigma\omega i)]\}$$

Because of the diversity in design and analysis of the various studies, we assumed that the true effects being estimated would vary among the studies.[12] Thus, RR can be described with a fixed effects model (all study populations were similar) and a random effects model (the study population differed). The homogeneity of ln(RRi) was tested by Q test.

$$Q = \Sigma\omega i \times [\ln(RRi) - \ln(RR)]^2$$

Under the null hypothesis that all studies derive from the same population, Q will follow a chi-square (χ^2) distribution for df = k-1, where k is the total number of outcomes.

If the *p*-values from the χ^2 test were significant ($p < 0.05$), results from the random effects model were used to take into account variation among the studies. Since heterogeneity always exists, it would be more conservative (and hence more appropriate) to use the random effects model regardless of the results of statistical tests of significance. In the random effects model, the variance(RRi) described above was modified to variance(RRi)†.

$$\text{variance}(RRi)^{\dagger} = \text{variance}(RRi) + \tau^2$$

$$\tau^2 = [Q - (k-1)] / (\Sigma\omega i - \Sigma(\omega i)^2 / \Sigma\omega i)$$

Studies differed in a number of aspects of their design and execution. Besides the summary RR from total independent studies, several RRs after stratifying were also calculated using the method described above.

The potential for publication bias was examined by constructing a "funnel plot" in which the inverse of variance was plotted against its lnRR. We used a linear regression approach to measure funnel plot asymmetry on the natural logarithm scale of RR. The standard normal deviate, defined as the RR divided by its standard error, is regressed against the estimate's precision, the latter being defined as the inverse of the standard error.[13]

RESULTS

Our search resulted in 18 potential articles (Table 1).[14-31] Cohort studies investigating prostate cancer risk due to the consumption of milk or dairy products started from 1960 in an Adventists study. The findings were published in 1984,[14] followed in 1989.[15] Although these two early articles seemed to be independently designed, the samples covered the same population (California Adventists). Thus, the latter article was retained until indicated. Since four articles shared data from the Health Professionals Follow-up study,[19, 23, 26, 29] the most recent article was selected for analysis if the observed item was included in this article. Thus, except for cheese and milk analysis, other analysis used the data from the Michand article because more diary products were included.[26] Unfortunately, one study had to be excluded because it did not

Table 1. Characteristics of published cohort studies in relation to consumption of milk or dairy products and prostate cancer risk

First Author (year)	Area and study project	No. of Population	No. of Case	Identification of cases	Period of following-up	Person-year	Quantile Intake comparison [1]	Items RR (95% CI) [2] Trend *p*	Match or Adjustment [3]
Snowdon (1984) [14]	USA California (Adventists)	6763	99	Fatal cases	1960-1980	77765	3 ＜1, ＞3 glasses/d 3 ＜1, ＞3 days/w	Milk 2.4 (1.3-4.3) *p*=0.005 Cheese 1.5 (0.9-2.6) *p*=0.12	1
Mills (1989) [15]	USA California (Adventists)	14000	180	Confirmed incident cases	1976-1982	78000	3 Never, ≧Daily	Whole milk 0.80 (0.54-1.19) *p*=0.29	1
Thompson (1989) [16]	USA California	1776	54	Incident cases	1972, 1974 -1987		Data not shown	Whole milk 0.9 (0.5-1.3) *p*=0.29	1, 8, 10-12
Severson (1989) [17]	USA Hawaii (Japanese ancestry)	7999	174	Confirmed incident cases	1965, 1968 -1986	139727	3 ≦1, ≧5 times/w [4]	Milk 1.0 (0.73-1.38) Butter, margarine, cheese 1.47 (0.97-2.54) Ice cream 1.31 (0.84-2.03)	1
Hsing (1990) [18]	USA (The Lutheran Brotherhood Cohort)	17633	149	Fatal cases	1966-1986	286731	4 26,86-189 times/m	Dairy 1.0 (0.6-1.7)	1, 11
Giovannucci (1993) [19]	USA (Health professionals)	47855	126	Advanced cancers (stage C, D and fatal cases)	1986-1990	167166	5 2.9, 20.9g/d [5]	Dairy fat 1.06 (0.56-1.98) *p*=0.92	1, 6
Le Marchand (1994) [20]	USA Hawaii	20316	198	Invasive cancer	1975-1980		4 ≦1, ≧5 times/w	Milk 1.4 (1.0-2.1) *p*=0.04	1, 4, 5
Grönberg (1996) [21]	Sweden (same-sex twin)	9680 (1218)	406	Incidence cases (1959-1989)	1967-1989		4 0, 5-9 glasses/d	Milk 0.84 (0.44-1.57) *p*=0.76	1
Veierød (1997) [22]	Norway	25708	72	Incident cases	1977, 1983 -1992	319588	Data not shown	Milk No association *p*≥0.33	1
Giovannucci (1998) [23]	USA (Health professionals)	47781	[a] 423	[a] Extraprostatic (stage C or D) cases	1986-1994		3 0, ≧ glasses/d	Milk [a] 1.6 (1.2-2.21) *p*=0.002 Metastatic cancers 1.8 (1.2-2.8) *p*=0.01	1, 6, 8, 13
Schuurman (1999) [24]	Netherlands	58279 (1525)	642	Incident, microscopically confirmed primary cancers	1986-1992		5 74, 566 g/d [5] 5 2, 43 g/d [5]	Milk and its products [6] 1.12 (0.81-1.56) *p*= 0.02 Cheese 1.21 (0.87-1.70) *p*= 0.09	1, 3, 9

Chan (2000) [25]	Finland (Smoker)	27062	184	stage B-D cases	1985-1993		5 275, 1119g/d [5]	Dairy 1.1 (0.7-1.7) p= 0.74	1, 3, 8, 11, 13
Michaud (2001) [26]	USA (Health profes-sionals)	47780	[b] 536 [c] 249	[b] Stage C, D and fatal cases [c] Stage D and fatal case	1986-1996		5 ＜19, ＞69 g/d (Dry weight)	Dairy products [7] [b] 1.07 (0.88-1.3) p=0.46 [c] 1.04 (0.60-1.8) p=0.76 Death cases 1.13 (0.77-1.7) p=0.93	1, 6, 7, 13
Chan (2001) [27]	USA (Physicians)	20885	1012	Incident self-reported cases, (99.1% was confirmed)	1984-1995		5 ≦0.5, ＞2.5 servings/d	Diary products 1.27 (0.97-1.66) p=0.14	1, 7, 8, 11, 13
Rodriguez (2003) [28]	USA	65321	[d] 3811 [e] 569	[d] Verified incident cases [e] Advanced (stage C2 and D) cases	1992, 1993 -2001	404393	5 ＜3/w, ≧4 servings /d	Diary [d] 1.1 (0.9-1.3) p=0.38 [e] 0.9 (0.5-1.4) [k] p=0.95	1-3, 6, 9, 14
Leitzmann (2004) [29]	USA (Health profes-sionals)	47866	448	Advanced cases	1986-2000	598321	5 ＜1/m, ≧1 time /d	Cheese 1.19 (0.66-2.13) p=0.25 Skim milk 1.07 (0.82-1.39) p=0.50	1, 2, 6-11, 13, 15
Tseng (2005) [30]	USA (NHANES I [8])	3612	131	Identified cases	1982, 1984 - 1992	27814	3 ＜5, ≧21 servings /w 3 ＜0.5, ≧14 servings /w 3 ＜0.25, ≧4 servings /w	Dairy [9] 2.2 (1.2-3.9) p=0.05 Total milk 1.8 (1.1-2.9) p=0.03 Cheese 1.1 (0.6-1.9)	1-4, 6, 7, 11, 12
Kesse (2006) [31]	French (SU.VI.MAX study [10])	2776	69	Identified cases	1994-2003		4 ＜160, ＞396 g/d 4 ＜25, ＞253 g/d 4 ＜25, ＞71 g/d	Dairy 1.35 (1.02-1.78) p=0.12 Milk 1.13 (0.54-2.34) p=0.59 Cheese 0.90 (0.42-1.91) p=0.92	1, 6-8, 11, 12, 14, 16

1: Intake comparison is the comparison of highest quantile to lowest one. 2: RR and 95 % CI extracted from these studies is what compared the highest with the lowest quantile of consumption and reflected the greatest degree of control for confounders. 3: 1.Age; 2.Race; 3.Education; 4.Region; 5.Income; 6.Energy; 7.Activity; 8.BMI; 9.Family history; 10.History of diabetes; 11.Smoking; 12.Cholesterol; 13.Some foods; 14.Fat; 15.Vasectomy; 16.Occupation. 4: w:week; m:month; d:day. 5: the value is median intake. 6. Fermented whole milk: RR per 50 g = 0.87 (0.76-1.00) for overall prostate cancer risk and RR per 50 g = 0.84, (0.66-1.05) for advanced tumors. Whole yoghurt: RR per 50 g increment = 0.88, (0.76-1.01). Cheese: RR per 20 g = 1.20, (1.06-1.37) for localized prostate tumors. 7: Intake of dairy categories in relation to metastatic prostate cancer risk (stage D and fatal) were included: Butter 1.28 (0.88-1.9); Ice-cream 1.18 (0.65-1.8); Skim or low fat milk 1.37 (0.90-1.5); Whole milk 1.12 (0.70-1.8); Cottage or ricotta cheese 1.04 (0.74-1.5); Other cheese 1.15 (0.76-1.7); Cream cheese 1.15 (0.77-1.7). All of trend p>0.2. 8: The first National Health and Nutrition Examination Survey. 9: Low-fat milk 1.5 (1.1-2.2), p=0.02; Ice cream 1.0 (0.7-1.5), p=0.96; Cream 0.9 (0.6-1.3); Yogurt 1.0 (0.6-1.9). 10: The France prospective Supplementation en Vitamines et Mineraux Antioxydants study. ∗ The superscript (a-e) in some items indicated that this RR came from cases with the same superscript.

Table 2. Summary RR and 95% CIs of prostate cancer risk and the consumption of milk or dairy products in different types of cohort studies

Subgroup	N	Total Cases	Total population	RR (95% CI)
Total independent studies	13	7546	297119	1.13 (1.02-1.24)
Studies except nested case-control studies	11	6498	229160	1.14 (1.02-1.27)
Studies used milk as item	8	1579	100788	1.21 (1.00-1.47)
Studies used dairy products as item	9	6708	251347	1.18 (1.07-1.30)
Studies used cheese as item	5	1389	119296	1.18 (1.03-1.32)
Studies claimed excluding stage A1	6	5890	198997	1.13 (1.02-1.26)
Studies including advanced stages	3	1303	133417	1.11 (1.00-1.24)
Study conducted in USA	9	6245	199322	1.11 (1.01-1.22)
Studies adjusted for total energy	6	2244	167436	1.17 (1.03-1.29)
Studies whose FFQ was validated	7	3193	232619	1.13 (1.02-1.26)
Studies whose response >75%	11	7223	271487	1.14 (1.02-1.28)
Studies whose follow-up ended after 1991	6	2725	222103	1.14 (1.03-1.28)

provide RR and 95% CI or any information that allowed for their calculation .[22] Finally, thirteen independent studies were entered into our meta-analysis,[15-18,20,21,24-28,30] of which two studies were nested case-control studies.[21,24]

Of all 13 studies, nine were carried out in the United States, and the other four in Western Europe. The number of cases in these cohort studies ranged from 54 to 3811. The largest population enrolled was 65321 in the Rodriguez study, followed by 58279 in the Schuurman study, where only 1525 subcohort members were retained for analysis (nested case-control study). Ultimately, these 13 studies included a total of 7546 cases and 297119 participants. The period of follow-up ranged from 4 to 23 years. All the studies used a food-frequency questionnaire (FFQ) to obtain diet information. Milk as an item was observed in 8 studies and dairy products in 9 studies. All the studies analyzed the relationship between prostate cancer risk and the consumption of milk or dairy products by partitioning intake, 4 by tertiles, 4 by quartiles and 5 by quintiles. Although different age groups were selected, age was adjusted in each study. The more recent studies usually incorporated more adjustments in their designs. The information of person-year was lacking in some articles although this did not mean that RR did not be calculated from person-year.

In these 13 studies, ten studies had RR values greater than 1. Two study found a positive relationship between milk consumption and prostate cancer risk with RR = 1.4, 95% CI = 1.0-2.1, [20] and RR = 1.8, 95% CI = 1.1-2.9.[30] Also, two studies found a positive relationship between dairy consumption and prostate cancer risk with RR = 2.2, 95% CI = 1.2-3.9, [30] and RR=1.35, 95% CI = 1.02-1.78 [31] when comparing the extreme quantiles. The other one observed a positive trend in prostate cancer risk for the consumption of dairy products (p = 0.02).[24] In that study, the RR in the fourth quintile of dairy products consumption was significantly increased (RR = 1.63, 95% CI = 1.2-2.2). Two articles that reported positive relationships were not included in the final analysis.[14,23] The recent articles for the same studies did not show positive associations because of the change of outcome from death to incidence or exposure from milk to dairy products. Cheese was observed in five studies with no significantly positive association (all RR>1).[14,24,29,30,31] However, no study reported any inverse relationship between the consumption of milk and dairy products and prostate cancer risk. Figure 1 shows the RR and 95% CI of each study when comparing the extreme quantile of consumption. Combining these 13 studies using the meta-analysis described above, the summary RR was 1.13 with a 95% CI of 1.02-1.24.

Since bias is a problem, an informative approach is to use broad inclusion criteria for studies and then to perform analysis relating to be suspected source of bias.[32] The effects of consumption of milk and dairy products on prostate cancer risk through subgroups of studies are shown in Table 2. When studies were stratified by milk and dairy products, RR increase to 1.21 (95% CI = 1.00-1.47) for milk and 1.18 (95% CI = 1.07-1.30) for dairy products. The summary RR in the studies that used cheese as an item was 1.78 (95% CI = 1.03-1.32) when combining five studies.

In the five most recent studies, the exposure was set to dairy products and the consumption was partitioned by

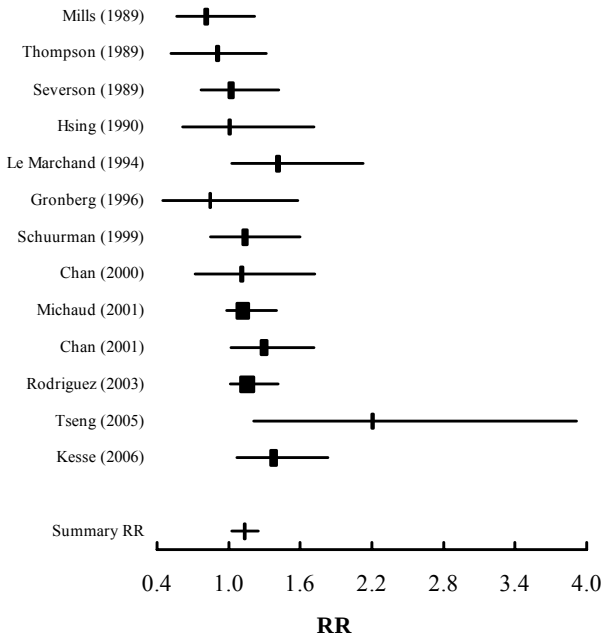

Figure 1. RR estimates and 95% CIs of prostate cancer in association with the consumption of milk or dairy products. The black rectangles and horizontal lines correspond to RR and 95% CI of the cohort studies when comparing the highest vs. the lowest quantile. The area of black rectangles reflects the study-specific weight (inverse of the variance). The diamond represents the summary RR =1.10 and 95% CI of 1.01-1.21.

quintile.[24-28] This provided us with a chance to observe the dose-response relationship of dairy consumption to prostate cancer risk although the quantiles were not strictly identical. The RR of prostate cancer significantly increased with higher quantile (Fig 2). As compared with the lowest quantile, the second to fifth quantiles had RRs of 1.03 (95% CI = 0.95-1.12), 1.07 (95% CI = 0.98-1.15), 1.12 (95% CI = 1.01-1.23) and 1.12 (95% CI = 1.00-1.25), respectively ($p < 0.01$ for linear trend).

As shown in Figure 3, the funnel plot did not show strong evidence for publication bias in these cohort studies. The test of linear regression showed the plot remained symmertrical (intercept = -0.62 with a 95% CI = -1.94-0.78, $p = 0.45$).

DISCUSSION

Milk is considered to be the only foodstuff that contains all of the different substances known to be essential for human nutrition.[33] To our surprise, our quantitative analysis for the published cohort studies suggested a statistically significant 10% increase of prostate cancer risk for the consumption of milk and dairy products. One should not belittle this 10% increase; it implies a large population at risk of prostate cancer when considering the high incidence of this disease.

When interpreting these data, however, several factors must be considered. Meta-analysis of observational studies poses particular challenges because of inherent biases and differences in study designs.[34] In the present study, two major problems arose from the exposure (milk and dairy products) and the outcome (prostate cancer). Because milk and dairy products are a heterogeneous group of foods, it may not be appropriate to consider them as a single exposure in relation to prostate cancer. If milk and dairy products are divided into individual items, the

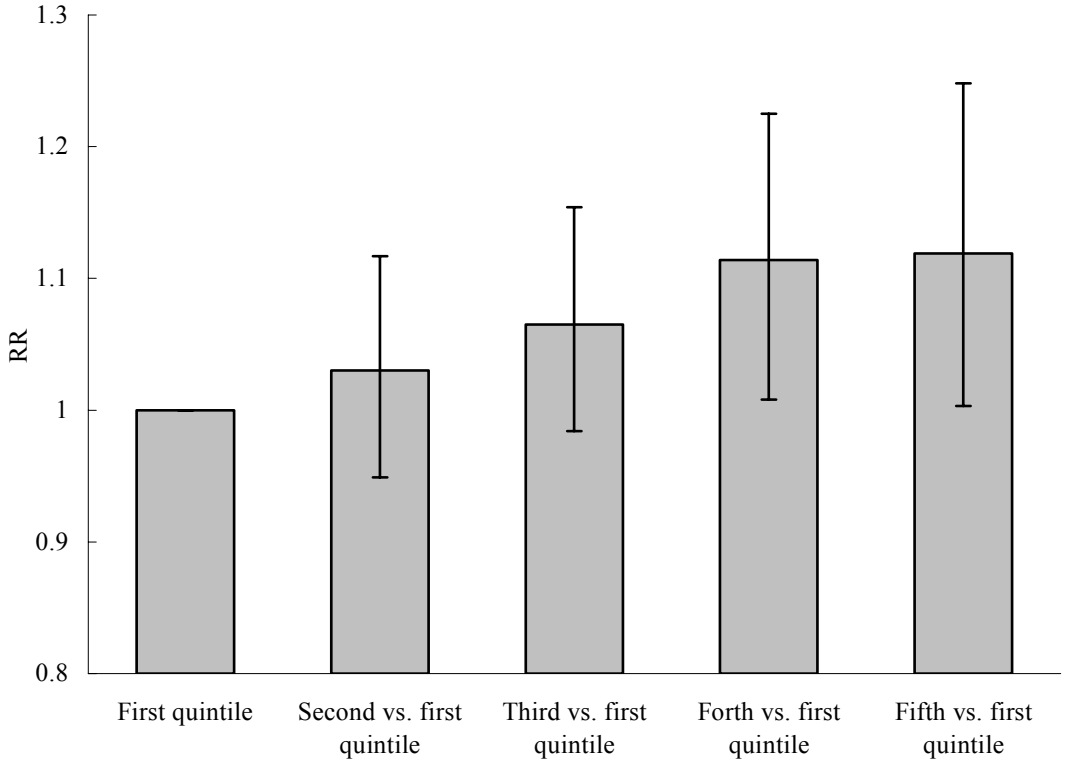

Figure 2. The RR and 95% CI for prostate cancer as compared the lowest quantile with the second to fifth quantiles when combining the five most recent studies that was partitioned by quintile. The RR was 1.03 (95% CI = 0.95-1.12), 1.07 (95% CI = 0.98-1.15), 1.12 (95% CI = 1.01-1.23) and 1.12 (95% CI = 1.00-1.25), respectively ($p < 0.01$ for linear trend).

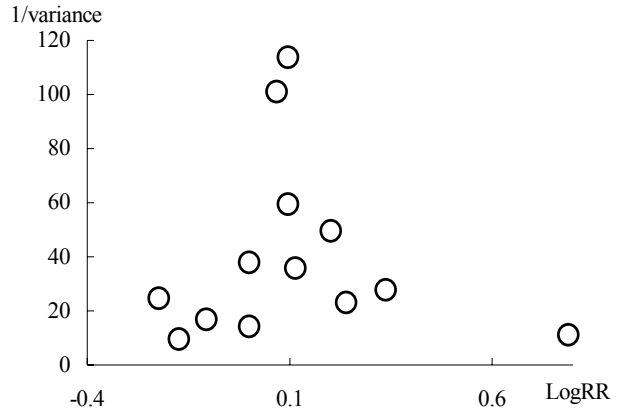

Figure 3. Funnel plot of studies of consumption of milk or dairy products and prostate cancer risk. The funnel plot did not show strong evidence for publication bias in these cohort studies and the text of linear regression showed the plot remained symmertrical (intercept = -0.59 with 95% CI = -1.90 – 0.73, P =0.41).

analysis will be impossible due to the lack of sufficient specific information. Therefore, we separated the studies into two subgroups: one using milk and the other using dairy products. We found greater RRs in both subgroups than that from the combined studies. Dairy consumption even showed a dose-response relationship for prostate cancer risk when combining the studies that partitioned the consumption by quintiles. On the other hand, all of these studies were conducted in Western countries where milk and dairy products are highly consumed. It was not surprising that the amounts of highest and lowest quantiles of consumption of each study did not vary much. Thus, the RR calculated using the data of the highest vs. the lowest quantile in our analysis is reliable.

In the previous study with case-control studies, all of the original data were obtained from confirmed prostate cancer cases and did not refer to the stage.[9] Beyond our expectation, this was not so in the combination of cohort studies because almost all studies provided cases with different groups of disease stages. The summary RR relies on the assumption that milk and dairy products have the similar effects of every stage of prostate cancer. However, it remains unclear whether every stage of this disease has the same etiological features.[25] To avoid the interference of disease stage, we re-analyzed the studies that claimed to exclude stage A1 because stage A1 trends to be relatively innocuous and is detected incidentally at surgery for benign prostate hyperplasia.[26] The result (RR = 1.13, 95% CI = 1.02-1.26) was similar to that for the total combined studies. When the stage was further narrowed to advanced prostate cancer, the RR changed to 1.11 with 95% CI =1.00-1.24 in the three remaining studies. Disease stage is thus not likely to affect the evaluation of milk and dairy products for prostate cancer risk in the present analysis.

The other problem that may confound all meta-analyses is publication bias. In the present analysis, the funnel plot and its test of linear regression showed that there was little evidence of publication bias. In fact, a cohort study, no matter what the result is, should have a chance to be published. One study that could not be incorporated in this analysis described that milk intake was not associated significantly with incidence of prostate cancer.[22] That study contained only 72 cases, accounting for approximately 1% of the total cases, and it should not affect the analysis much even if the absence.

The geographical region was relatively homogeneous in the present analysis because all studies came from Western countries. If the area were limited to the United States, there is no change of the RR and 95% CI. For meta-analysis, homogeneity of studies is desirable for the statistician. However, for the research of cancer epidemiology, the homogeneity (narrow range) among people living in developed countries, which represents only a fraction of the global population and dietary patterns, may result in an incomplete understanding of the relationship between many factors and cancer risk.[35] Thus, we also searched in the Chinese Journal Database (CNKI) for relative studies published in Chinese. We did not find a cohort study to observe the relationship between milk consumption and prostate cancer risk. There was only one case-control study where milk consumption increased prostate cancer (p<0.05%). Epidemiological studies in developing countries should be encouraged.

Meta-analysis, whatever modern model is used, cannot resolve the confounding variables that were not adjusted in the original study design. Comparing with the previous study using software,[9] the strength of the present analysis is that the effects of confounding variables are taken into consideration by using adjusted RR in the calculation of a summary RR. However, the degree of adjustment was different in the studies. For example, total energy was adjusted only in most recent six studies and their combined RR was 1.17 (95% CI= 1.03-1.29).[26-31] Prostate specific antigen (PSA) screening was widely performed in Western countries since the beginning of 1990s.[36] PSA screening may increase the pool of indolent prostate cancer. Unfortunately, the information of PSA screening was ignored by all studies except Michaud's report with a similar percentage among men consuming low and high intake of dairy products (63.5% vs. 63.0%). If we assumed the participants in the study whose follow-up ended after 1991 had a chance for PSA screening, the combined RR for these 5 studies was 1.12 with 95% CI of 1.01-1.25.[24-28]

The positive association between the consumption of milk and dairy products and prostate cancer risk is biologically plausible. Milk and dairy products account for a substantial proportion of the total fat and saturated fat intake in the Western diet. For example, saturated fat in the diet that comes from dairy products is about 31% in America and 50% in Sweden.[37,38] Dietary fat has been postulated to increase the androgen level that is associated with prostate cancer risk.[39, 40] Among these cohort studies, one study that found positive association contributed the risk to high-fat animal products.[20] However, most of these cohort studies did not consider fat as a risk factor for prostate cancer since no association was found for high-fat animal products, such as milk and dairy products. The most recent published study even found that prostate cancer risk was elevated only for low-fat milk and not for whole milk.[30] The other one study also found that risk was increased significantly for subjects drinking skim milk to those drinking whole milk although the RRs of

skim milk and whole milk for prostate cancer were not available in that study.[22] Thus, the role of fat on the incidence of prostate cancer is not yet clear. Fat in milk and dairy products is a likely factor for prostate cancer risk; but it cannot explain all of the causes.

Not only androgen, but also estrogen is evoked by fat.[41,42] Furthermore, milk itself contains considerable amounts of estrogens due to commercial milk is mainly produced by pregnant cows in developed countries.[43-46] Because 17β-estradiol, an estrogen, is a carcinogen for prostate cancer, estrogen contained in milk and evoked by milk fat should not be ignored when considering milk as a risk factor for prostate cancer. Moreover, cows' milk contains high levels of insulin-like growth factor (IGF)-I that also contributes to prostate cancer risk. In a human study, plasma IGF-I concentration increased by 10% when healthy subjects consumed cows' milk.[47] In our previous study, commercial low-fat milk promoted the development of DMBA-induced mammary tumors, another hormone-dependent cancer, in rats. The high levels of estrogen and IGF-I in milk were considered to be responsible for this promotional effect.[44] In fact, all dietary effects on hormone-dependent cancer, such as breast cancer in women and prostate cancer in men, are probably mediated by the hormonal mechanism.[48]

The other hypotheses suggested an increased risk of prostate cancer associated with the consumption of milk and dairy products focused on calcium. The strongest evidence came from the Health Professional Follow-up Study, which has a comprehensive dietary assessment of calcium from food and other sources. In this study, men who consumed more than 2000 mg of calcium had a RR of 4.6 (95% CI = 1.9-11.0) for metastatic and fatal prostate cancer compared with men consuming less than 500 mg.[23] They further analyzed the calcium in dairy products and found the significantly increased risk for metastatic prostate cancer arising from dairy products intake came to have no association after controlling for calcium and some fatty acids.[26] As a mechanism, some researchers proposed that high calcium intake suppressed the conversion of 25(OH) vitamin D to $1,25(OH)_2$ vitamin D, which has an anti-tumor effect against prostate cancer.[22,24,25]

In conclusion, we found a positive association between high consumption of milk and dairy products and prostate cancer risk when analyzing published cohort studies with meta-analysis. This finding verified our previous meta-analysis using case-control studies. Although no one can deny that humans gain great benefit from milk and dairy products, the balance between advantages and disadvantages of the consumption of milk and dairy products should be investigated as an important field in public heath.

ACKNOWEDGEMENTS

Li-Qiang Qin is funded by the Japan Society for the Promotion of Science (JSPS) postdoctoral fellowship for foreign researcher.

This research was supported in part by a grant from National Natural Science Foundation of China (No. 30471448) to Dr. Pei-Yu Wang, and by a grant from Ministry of Education, science, Sports and Culture of Japan (No. 12470083) to Dr. Akio Sato.

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Original Article

Milk consumption is a risk factor for prostate cancer in Western countries: evidence from cohort studies

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牛奶消费与前列腺癌：西方国家列队研究的 meta 分析

我们曾经利用 meta 分析研究了病例-对照研究，发现牛奶消费和前列腺癌发生存在正相关。本研究中，我们收集了 1966 年到 2006 年发表的队列研究，用 meta 分析的方法进一步研究牛奶及奶制品消费和前列腺癌之间的总相对危险度(RR)。我们共搜索到 18 篇相关文章，其中含有的 13 个独立研究被用于本次分析。比较最高和最低消费组后得到总 RR 为 1.13(95%可信区间 = 1.02-1.24)。经分层分析后仍存在正相关。单独分析研究对象被分成 5 个剂量组的队列研究则发现 RR 值随消费量的上升而增强。我们还评价了诸如奶制品分类、癌症分级和出版偏倚对 meta 分析的影响。本研究提示牛奶和奶制品消费增加了患前列腺癌的危险性。其机制可能与牛奶和奶制品中的脂肪、激素以及钙有关。

关健字：牛奶、奶制品、前列腺癌、meta 分析、队列研究。