An Up-to-date Meta-analysis of Coffee Consumption and Risk of Prostate Cancer

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Purpose: Results of the association between coffee consumption (CC) and the risk of prostate cancer (PC) are still controversy. Based on published relevant studies, we conducted an up-to-date meta-analysis to investigate this issue.

Materials and Methods: The protocol used in this article is in accordance with the PRISMA checklist. Eligible studies were screened and retrieved by using PUBMED and EMBASE as well as manual review of references up to July 2016. We calculated the pooled relative risk (RR) with 95% confidence interval (CI) with random effect models. The dose-response relationship was assessed by generalized least-squares trend estimation analysis.

Results: Totally, we included twenty-eight studies (14 case-control and 14 cohort studies) on CC with 42399 PC patients for the final meta-analysis. No significant association of PC was found for high versus non/lowest CC, with RR = 1.07 (95% CI: 0.96-1.18). In subgroup meta-analysis by study design, there were no significant positive associations between CC and PC in case-control studies (RR = 1.19, 95% CI: 1.05-1.35) or in the cohort studies (RR = 0.97, 95% CI: 0.84-1.12). Additionally, RR with different quality of studies were respectively 1.15 (95% CI: 0.99-1.34) and 1.28 (95% CI: 1.03-1.58) for high and low quality in the case-control studies; while were respectively 1.02 (95% CI: 0.88-1.20) and 0.81 (95% CI: 0.57-1.14) in the cohort studies. When analyzed by geographic area, we found no association between CC and PC, with RR = 1.06 (95% CI: 0.86-1.30) for 10 studies from Europe, 1.06 (95% CI: 0.94-1.20) for 13 studies conducted in America; 1.12 (95% CI: 0.70-1.79) for 4 studies from Asia. However, in subgroup analysis by subtype of the disease, there was a significant negative (beneficial) association in the localized PC (RR = 0.90, 95% CI: 0.84-0.97), but not for the advanced PC (RR = 0.90, 95% CI: 0.70-1.16). Additionally, RR = 0.99 (95% CI: 0.98-0.99) for an increment of one cup per day of coffee intake shows significant association with the localized PC.

Conclusion: Our results indicate that CC has no harmful effect on PC. On the contrary, it has an effect on reducing the localized PC risk. Further prospective cohort studies of high quality are required to clarify this relationship.

Keywords: prostate cancer; coffee consumption; dose-response; stage-specific; meta-analysis.

INTRODUCTION

Since the introduction of prostate specific antigen testing, the rate of men diagnosed with prostate cancer (PC) has increased, which makes PC the most frequently diagnosed tumor and the second leading cause of death from cancer in men[(1)]. In General, the incidence of PC in Western countries is approximately six-fold higher than that of non-Western countries. Some of this discrepancy may be caused by increased screening, but it has been hypothesized that differences in dietary intake may also account for it, though much of the research has no explicit conclusions[(2-4)].

Coffee is one of the most widely consumed beverages in the world. It is a complex chemical mixture that contains many compounds, which have been suggested to have potential genotoxic, mutagenic and anti-mutagenic activities in lower organisms[(5)]. Coffee is also a main source of dietary methylxanthines, e.g. caffeine[(6)]. It has been reported that caffeine has obvious effects on a variety of physiologic, cellular and molecular systems, which is fundamental in basic and clinical research[(7)]. Since the 1980s, many epidemiologic studies have estimated the association between coffee consumption (CC) and PC risk with inconsistent results. So far, meta-analyses have been conducted on this issue, yet with opposite conclusions[(8-10)]. However, most of them were methodologically defective—neither of them carried out meta-regressions to examine dose-response analysis, nor did they include all the published studies available at the time of their compilations[(11)]. Furthermore, some large prospective cohort studies with high quality have examined the association between CC and PC risk as well as stage-specific (localized or advanced). Additionally, we used multiple subgroup analysis to assess the association between CC and PC, which is different from the previous meta-analysis, and we used generalized least-squares trend estimation analysis to assess the dose-response relationship, which could complicate the interpretation of the pooled results.

Therefore, the aim of the present study is to provide a quantitative assessment on this topic, we systematically performed a meta-analysis by summarizing all available data of both case-control and cohort studies, besides, we also conducted the meta-analysis to see the

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Table 1. Characteristics of studies included in the meta-analysis of coffee consumption and prostate cancer risk

Authors (publication year)	Study Design	Study Country	Study period	Cases/ noncases	Coffee consumption	Adjusted OR/RR (95% CI) All PCA	Local PCA	Advanced PCA	NOS score	Adjustments
Talamini et al. 1992 [32]	Case-control Hospital based	Italy	1986-1990	271/685	1 Low	1.0	NA	NA	6	Age, area of residence, education, and BMI.
					2 Inter-mediate	1.12 (0.78-1.62)	NA	NA		
					3 High	1.34 (0.93-1.93)	NA	NA		
Slattery et al. 1993 [33]	Case-control Population based	USA	1983-1986	362/685 /week	0 cups/ week	1.00	NA	1.00	5	Age
					1-20 cups /week	0.99 (0.68-1.47)	NA	1.39 (0.67-2.87)		
					>20 cups /week	1.09 (0.75-1.60)	NA	1.04 (0.47-2.26)		
Gronberg et al. 1996 [34]	Case-control Population based	Sweden	1959-1989	406/1218	0 cups/day	1.00	NA	NA	7	Specific food items, smoking habits and alcoholic consumption
					1-2 cups/day	1.77 (0.65-5.09)	NA	NA		
				3-5 cups/day (0.78-5.46)	1.99	NA	NA			
					6-9 cups/day	1.91 (0.73-5.30)	NA	NA		
Key et al. 1997 [35]	Case-control Population based	England	1989-1992	328/328	0 cups/day	1.00	NA	NA	7	Energy intake
					1 cups/day	0.92 (0.60-1.42)	NA	NA		
					2 cups/day	1.41 (0.89-2.21)	NA	NA		
					≥ 3 cups/day	0.94 (0.59-1.51)	NA	NA		
Jain et al. 1998 [36]	Case-control Population based	Canada	1989-1993	617/636	0 g/day	1.00	NA	NA	6	Age and total energy intake
					0-500 g/day	0.84 (0.58-1.22)	NA	NA		
					> 500 g/day	0.97 (0.65-1.44)	NA	NA		
Hsieh et al. 1999 [37]	Case-control Hospital based	Greece	1994-1997	320/246	0 cups/day	1.00	NA	NA	5	Age, height, BMI, and years of schooling
					< 1 cups/day	0.38 (0.15-0.99)	NA	NA		
					1-2 cups/day	0.72 (0.35-1.45)	NA	NA		
					2-3 cups/day	0.57 (0.29-1.12)	NA	NA		
					> 3 cups/day	1.15 (0.53-2.47)	NA	NA		
Villeneuve et al. 1999 [19]	Case-control Population based	Canada	1994-1997	1623/1623	0 cups/day	1.0	NA	NA	6	Age, province of residence, race, years since quitting smoking, cigarette pack-years, alcohol, grains
					< 1 cups/day	0.8 (0.6-1.1)	NA	NA		
					1-4 cups/day	1.0 (0.7-1.3)	NA	NA		
					≥4 cups/day	1.1 (0.8-1.5)	NA	NA		
Sharpe et al. 2002 [37]	Case-control Population based	Canada	1979-1985	399/476	0 drinks/day	1.00	NA	NA	5	Age, ethnicity, respondent status, family income, BMI, cumulative cigarette smoking, alcohol consumption
					1-2 drinks/day	1.1 (0.6-1.9)	NA	NA		
					3-4 drinks/day	1.1 (0.6-1.9)	NA	NA		
					≥ 5 drinks/day	0.9 (0.5-1.7)	NA	NA		
Chen et al. 2005 [38]	Case-control Hospital based	China	1996-1998	237/481	No	1.00	NA	NA	6	Age and BMI
					Yes	1.88 (1.07-3.30)	NA	NA		
Gallus et al. 2007 [39]	Case-control Hospital based	Italy	1991-2002	219/431	1st Tertile	1.0	NA	NA	5	Age, study center, education, occupational physical activity at 30 –39 years, BMI, family history, and total energy intake
					2nd Tertile	1.3 (0.8-2.1)	NA	NA		
					3rd Tertile	1.9 (1.2-3.0)	NA	NA		
Ganesh et al. 2011 [40]	Case-control Hospital based	India	1999-2001	123/167	No	1.0	NA	NA	5	Age, religion and education
					Yes	1.3 (0.6-2.7)	NA	NA		

Deneo-Pellegrini *et al.* 2012 [41]	Case-control Hospital based	Uruguay	1996-2004	326/652	Tertile I	1.0	NA	NA	5	Age, residence, urban/rural status, education, family history of prostate cancer among first degree relatives, BMI and total energy intake
					Tertile II	1.54 (0.91-2.59)	NA	NA		
					Tertile III	1.37 (0.82-2.29)	NA	NA		
Geybels et al. 2013 [22]	Case-control Population-based	USA	2002-2005	892/863	≤ 1/week	1.0	1.0	1.0	6	age,race, first-degree family history of prostate cancer, smoking status, and history of prostate cancer screening
					2-6/week	1.22 (0.88-1.69)	1.25 (0.89-1.76)	1.01 (0.55-1.83)		
					1 /day	1.13 (0.84-1.51)	1.07 (0.97-1.47)	1.27 (0.77-2.11)		
					2-3 /day	1.16 (0.90-1.50)	1.13 (0.86-1.49)	1.23 (0.78-1.61)		
					≥ 4/day	1.16 (0.82-1.63)	1.12 (0.78-1.93)	1.33 (0.74-2.38)		
Wilson et al. 2013 [18]	Case-control Population- based	Sweden	2001-2002	1499/1112	< 1 cup/day	1.00	1.00	1.00	7	age, region, smoking, BMI, education, and intake of calcium, zinc, and total energy
					1-<2 cups/day	0.97 (0.62-1.52)	0.88 (0.59-1.31)	0.70 (0.40-1.23)		
					2-<4 cups/day	0.98 (0.65-1.49)	0.98 (0.71-1.35)	0.83 (0.53-1.29)		
					4-5 cups/day	1.06 (0.69-1.62)	1.01 (0.72-1.42)	1.02 (0.64-1.62)		
					> 5 cups/day	0.97 (0.60-1.57)	0.89 (0.59-1.35)	0.73 (0.41-1.30)		
Jacobsen et al. 1986 [13]	Cohort	Norway	1967-1969	205/13664	≤2 cups/day	1.00	NA	NA	6	Age, residence, cigarette smoking
					3-4 cups/day	0.83 (0.59-1.15)	NA	NA		
					5-6 cups/day	0.78 (0.53-1.15)	NA	NA		
					≥7 cups/day	0.74 (0.47-1.25)	NA	NA		
Nomura et al. 1986 [14]	Cohort	USA	1965-1968	108/7355	0 cups/day	1.00	NA	NA	8	Age
					1-2 cups/day	1.21 (1.02-1.43)	NA	NA		
					3-4 cups/day	1.06 (0.88-1.26)	NA	NA		
					>5 cups/day	1.43 (1.20-1.69)	NA	NA		
Severson et al. 1989 [42]	Cohort	USA	1965-1978	174/7999	≤1 time /week	1.00	NA	NA	8	Age
					2-4 times /week	0.96 (0.39-2.37)	NA	NA		
					≥5 times/ week	0.92 (0.59-1.44)	NA	NA		
Hsing et al. 1990 [43]	Cohort	USA	1966-1986	149/17633	≤3 cups/day	1.00	NA	NA	6	Age
					3-4 cups/day	0.8 (0.6-1.2)	NA	NA		
					≥5 cups/day	1.0 (0.6-1.6)	NA	NA		
Marchand et al. 1994 [44]	Cohort	USA	1975-1980	198/20316	1 Quantile	1.0	NA	NA	8	Age, ethnicity and income
					2 Quantile	0.9 (0.6-1.4)	NA	NA		
					3 Quantile	1.2 (0.8-1.8)	NA	NA		
					4 Quantile	1.1 (0.7-1.7)	NA	NA		
Stensvold et al. 1994 [45]	Cohort	Norway	1977-1982	177/21735	≤2 cups/day	1.00	NA	NA	7	Age, cigarettes per day and county of residence
					3-4 cups/day	0.3 (0.13-1.10)	NA	NA		
					5-6 cups/day	0.6 (0.30-1.71)	NA	NA		
					≥7 cups/day	0.4 (0.23-1.44)	NA	NA		
Ellison et al. 2000 [46]	Cohort	Canada	1970-1993	145/3400	0 ml/day	1.00	NA	NA	7	Five-year age group and wine consumption
					0-250 ml/day	1.14 (0.66-1.97)	NA	NA		
					250-500 ml/day	1.42 (0.80-2.52)	NA	NA		
					500-700 ml/day	1.35 (0.77-2.61)	NA	NA		
					> 750 ml/day	1.42 (0.77-2.61)	NA	NA		
Iso et al. 2007 [47]	Cohort	Japan	1988-1997	161/43500	≤1-2/month	1.00	NA	NA	8	Age and area of study
					1-4/week	0.96 (0.48-1.92)	NA	NA		
					1/day	1.19 (0.71-1.97)	NA	NA		
					≥2/day	1.13 (0.73-1.75)		NA	NA	

Nilsson et al. 2010 [20]	Cohort	Sweden	1992-2007	653/32425	< 1 occ/day	1.00	NA	NA	8	Age, BMI, smoking, education and recreational physical activity
					1-3 occ/day	0.92 (0.70-1.21)	NA	NA		
					≥4 occ/day	1.03 (0.77-1.38)	NA	NA		
Wilson et al. 2011 [15]	Cohort	USA	1986-2006	5035/47911	none	1.00	1.00	1.00	8	
					< 1 cup/day	0.94 (0.85-1.05)	1.01 (0.88-1.15)	0.81 (0.64-1.02)		
					1-3 cups/day	0.94 (0.86-1.04)	0.94 (0.87-1.12)	0.99 (0.60-0.93)	0.75	Race, height, BMI, vigorous physical activity, smoking, diabetes, family history of prostate cancer, multivitamin use, intake of processed meat, tomato sauce, calcium, alpha linolenic acid, supple mental vitamin E, alcohol intake and history of PSA testing
					4-5 cups/day	0.93 (0.83-1.04)	1.02 (0.88-1.18)	0.73 (0.56-0.95)		
					≥6 cups/day	0.82 (0.68-0.98)	0.93 (0.74-1.16)	0.47 (0.28-0.77)		
Shafique et al. 2012 [21]	Cohort	England	1970-2007	318/6017	0 cups/day	1.00	NA	NA	8	Age at screening, cholesterol, systolic blood pressure, BMI, alcohol intake, tea consumption, smoking status, social class
					1-2 cups/day	0.84 (0.60-1.21)	NA	NA		
					≥3 cups/day	0.74 (0.47-1.16)	NA	NA		
Discacciati et al. 2013 [23]	Cohort	Sweden	1998-2010	3801/ 44613	0	NA	1.13 (0.93-1.27)		0.96 (0.68-1.35)	tea, alcohol, BMI, personal history of diabetes, family history of PCa, smoking status, physical activity education and total energy intake
					< 1cup/day	NA	1.00 (0.86-1.16)		0.97 (0.78-1.21)	
					1-3 cups /week	NA	1.00		1.00	
					4-5 cups/day	NA	0.93 (0.83-1.03)		0.95 (0.79-1.14)	
					≥ 6 cups/day	NA	0.81 (0.69-0.96)		0.87 (0.66-1.16)	
Bosire et al. 2013 [17]	Cohort	USA	1995-2007	23335/ 288391	0 cup/day	1.00	1.00	1.00	8	age, race, height, BMI, physical activity, smoking, history of diabetes, family history of prostate cancer , PSA testing, intakes of toma to sauce, alpha-linolenic acid, and total energy intake
					< 1 cup /day	1.03 (0.98-1.08)	1.03 (0.97-1.09)	1.10 (0.95-1.28)		
					1 cup /day	1.00 (0.95-1.06)	1.01 (0.95-1.07)	0.97 (0.83-1.14)		
					2-3 cups/day	1.00 (0.96-1.05)	1.01 (0.96-1.07)	0.98 (0.86-1.12)		
					4-5cups/day	1.00 (0.94-1.06)	0.99 (0.93-1.06)	1.08 (0.92-1.27)		
					≥ 6 cups/day	0.94 (0.87-1.02)	0.92 (0.84-1.01)	1.15 (0.92-1.43)		
Li et al. 2013 [16]	Cohort	Japan	1995-2005	318/18853	0 cups/day	1.0	1.0	1.0	7	age, education level, BMI, time engaging in sports or exercise, marital status, time status, family history of cancer, consumption of spent walking, smoking tea, job status, daily total energy intake, passive smoking, alcohol drinking, daily consumption of miso soup
					< 1 cup/day	0.81 (0.61-1.07)	0.89 (0.48-1.65)	1.26 (0.73-2.16)		
					1-2 cups/day	0.73 (0.53-1.01)	0.73 (0.61-2.20)	1.16 (0.38-1.39)	0.73	
					≥3 cups/day	0.63 (0.39-1.00)	0.54 (0.18-1.66)	0.90 (0.38-2.12)		

Abbreviations: OR/RR, odd ratio/rate ratio; C, confidence interval; NOS, Newcastle-Ottawa Scale; BMI, body mass index (kg/m^2); occ, occasion; PSA, prostate specific antigen; NA, not available, PCA; prostate cancer

Table 2. Summary relative risk estimates and 95% for coffee consumption and prostate cancer risk.

Study	No. of studies	No. of cases	Relative risk (95% CI)	P value	Heterogeneity test		
					Q	*P*	I2 (%)
Highest vs. lowest							
All studies	28	42399	1.07 (0.96-1.18)	0.228	54.40	0.001	52.2
Study design							
Case-control studies	14	7622	1.19(1.05-1.35)	0.005	12.12	0.518	0.0
Cohort studies	14	34777	0.97(0.84-1.12)	0.668	34.10	0.001	64.8
Hospital based case-control studies	6	1496	1.50 (1.21-1.85)	0.000	2.72	0.743	0.0
Population based case-control studies	8	6126	1.06 (0.91-1.23)	0.445	2.54	0.924	0.0
Study geographic area							
Europe	10	4396	1.06 (0.86-1.30)	0.586	16.60	0.055	45.8
America	13	33363	1.06 (0.94-1.20)	0.361	28.04	0.005	57.2
Asia	4	839	1.12 (0.70-1.79)	0.635	9.03	0.029	66.8
Methodological quality of study							
Case-control study							
High quality	8	5873	1.15 (0.99-1.34)	0.060	6.58	0.474	0.0
Low quality	6	1749	1.28 (1.03-1.58)	0.026	4.96	0.421	0.0
Cohort study							
High quality	8	6647	1.02 (0.88-1.20)	0.781	24.30	0.001	71.2
Low quality	5	994	0.81 (0.57-1.14)	0.221	7.46	0.114	46.4
Stage-specific							
Localized PCA	6	26064	0.90 (0.84-0.97)	0.006	4.07	0.539	0.0
Case-control studies	2	1745	1.01 (0.77-1.33)	0.922	0.67	0.413	0.0
Cohort studies	4	24319	0.90 (0.83-0.97)	0.004	2.65	0.448	0.0
Advanced PCA	7	5304	0.90 (0.70-1.16)	0.399	12.83	0.046	53.2
Case-control studies	3	584	0.99 (0.69-1.44)	0.976	2.07	0.356	3.2
Cohort studies	4	4720	0.84 (0.58-1.21)	0.340	10.71	0.013	72.0
Increment of 1 cup/day							
All studies	19	36985	0.99 (0.98-1.00)	0.046	56.21	0.542	0.0
Study design							
Case-control studies	9	6446	1.01 (0.95-1.06)	0.825	29.97	0.269	3.9
Cohort studies	10	30539	0.99 (0.98-1.00)	0.012	23.12	0.810	0.0
Stage-specific							
Localized PCA	6	26064	0.99 (0.98-0.99)	0.003	15.4	0.800	0.0
Case-control studies	2	1745	1.01 (0.96-1.06)	0.680	2.76	0.907	0.0
Cohort studies	4	24319	0.99 (0.98-0.99)	0.002	11.86	0.539	0.0
Advanced PCA	7	5304	0.98 (0.94-1.02)	0.410	27.62	0.231	0.2
Case-control studies	3	584	1.02 (0.96-1.08)	0.539	6.74	0.664	0.0
Cohort studies	4	4720	0.97 (0.91-1.02)	0.263	19.20	0.117	2.6

Abbreviations: CI, confidence interval; PCA, prostate cancer

relationship of CC with stage-specific prostate cancer incidence.

MATERIAL AND METHODS

Publication search

We systematically reviewed the literature by electronically searching PUBMED and EMBASE up to July 2016. The search terms included the keywords "coffee", "caffeine", "diet", combined with "prostate cancer", "prostate carcinoma", "prostate neoplasm". All of the references in the relevant articles were screened for any further articles that were not identified in the initial search. Two reviewers (JX and JC) independently searched and extracted the data according to the defined inclusion and exclusion criteria.

Inclusion and exclusion criteria

Inclusion criteria were as follows:(1) Studies had a case-control or cohort design;(2) The outcome of interest was primary prostate cancer;(3) The exposure of interest was CC; and(4) Relative risk (RR) and their 95% confidence intervals (CI) could be extracted or calculated from relevant articles. Exclusion criteria were as follows:(1) incomplete data availability;(2) duplicated or updated data;(3) non-inclusion of their own data, such as reviews, comments, editorials, letters and congress.

Data extraction

Two reviewers (JX and JC) independently extracted and recorded the following information: first author's surname, year of publication, study design, study country, follow-up period or study period, number of participants (cases or controls/subjects), the exposure to CC, the odds ratios (OR, from case-control studies) or rate ratios (RR, from cohort studies) estimated with 95% CI for each category of CC of all PC and stage-specific (localized or advanced), and variables adjusted for in the analysis . If 95% CI were not provided, but the numbers of cases and controls (or person-time) in exposure categories were reported[12-14], these data were used to calculate the standard error of the crude RR, and then approximate CI for the reported adjusted RR. For several RRs from age-adjusted model to different multivariate models[15-23], we chose the RRs from multivariate models with the most complete adjustment for potential confounders. Disagreements were resolved through consensus with a third reviewer (XJ).

Quality assessment of included studies

Two independent reviewers (JX and JC) systematically performed the methodological quality assessment of selected studies according to the Newcastle-Ottawa Scale (NOS)[24]. The quality criteria assessed were as follows: the representative and applicability of study groups, comparability of the groups, evaluation of outcomes, and adequacy of follow-up. Since standard criteria have not been stated, we defined scores as ≥6 for case-control

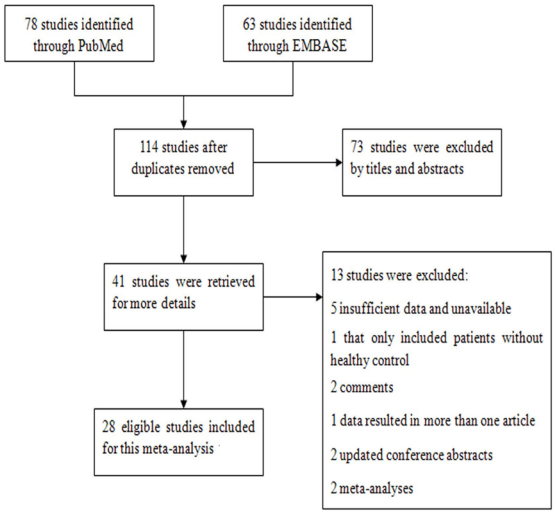

Figure 1. Flow diagram of the studies identified in the meta-analysis

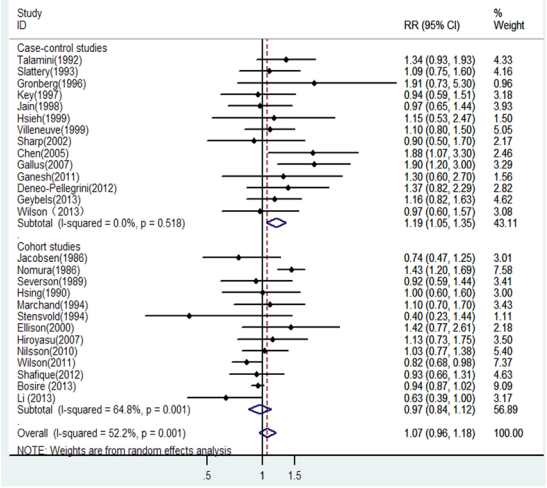

Figure 2. Forest plot of case-control and cohort studies assessing the association between high coffee consumption (high versus non/lowest) and prostate cancer risk. Horizontal lines indicate 95% confidence interval (CI); diamonds indicate summary relative risk estimate with its corresponding 95% CI.

studies and ≥8 for cohort studies being of high methodological quality, otherwise being of low quality[8].

Statistical analysis

Study-specific log (rate ratio) for cohort studies and log (OR) for case-control studies were combined to compute a pooled RR and its 95% CI for the highest versus non/lowest category of coffee consumption from each study with the Dersimonian and Larid random effects models[25]. The heterogeneity of effect size among studies was tested by Q statistics ($P < .10$ indicated the presence of heterogeneity), and inconsistency was quantified by I2 statistics (I2 > 50% is considered significant)[26,27]. In situations with substantial heterogeneity, the subgroup analysis was used to explore the sources of heterogeneity based on the characteristics of the studies (study design, geographic region, study quality, stage-specific), and a sensitivity analysis was performed to assess the stability of the results.

Based on the method developed by Greenland and Longnecker[28,29], we applied generalized least-squares trend estimation analysis to examine dose-response relationship between different categories of coffee intake using the random-effects model. For all studies, the median cups of CC for each category were calculated as the average consumption by assigning the midpoint of upper and lower boundaries. If the upper bound was not provided, we assumed that the average consumption had the same amplitude of intake as the preceding category. This method requires that the distributions of case patients and control subjects (or person-time) and the risk estimates with their variance estimates for at least three quantitative exposure categories, so studies providing no cutoff or median of coffee intake in each category, or reporting only two categories of exposure, or lacking the number of cases and non-cases in each exposure category were excluded. For studies using units or milliliter other than cups for consumption, we roughly converted them into cups per day as a standard measure (1 time/occasion/drink=1 cup, 125 ml= 1 cup, 250 g =1 cup).

Ultimately, we evaluated the possibility of publication bias through a funnel plot and with the Begg's and Egger's tests[30,31]. A two-tailed $P < .05$ was considered statistically significant. All statistical analyses were performed with STATA (version 11.0; Stata Crop).

RESULTS

Study characteristics

A total of 114 potentially eligible studies were initially identified, most of which were excluded because the exposure or endpoint was not relevant to our analysis. The study identification and selection progression were summarized in **Figure 1**. Finally, we identified 28 eligible studies in our meta-analysis,[12-23,32-47] including 14 case-control studies and 14 cohort studies. The former included 7622 cases of PC and 9603 controls, while the latter involved 34777 cases of PC and 573812 participants. Particularly, one study only reported the stage-specific RR but not all the PC[23]. Of these 28 studies, 13 were conducted in America (USA, Canada and Uruguay), 11 in Europe (Sweden, England, Greece, Italy and Norway) and 4 in Asia (China, India and Japan). Among the case-control studies, 6 used hospital-based controls and 8 applied population-based controls. The RRs of most studies were adjusted for age or body mass index (BMI, kg/m^2), which are the most likely confounder of relationship between coffee intake and PC. General characteristics in the studies included in this meta-analysis were shown in **Table 1**.

High versus non/lowest coffee consumption

Figure 2 and **Table 2** present the multivariable-adjusted RRs in each study and the pooled RR of PC for the highest versus non/lowest categories of coffee intake. The combined summary RR from all the studies was 1.07 (95% CI: 0.96-1.18, $P = .228$). In the subgroup analysis by study design, the summary RRs from case-control studies and cohort studies were respectively 1.19 (95% CI: 1.05-1.35, $P = .005$) and 0.97 (95% CI: 0.84-1.12, $P = .668$). When separating the hospital-based case-control studies from the population-based case-control

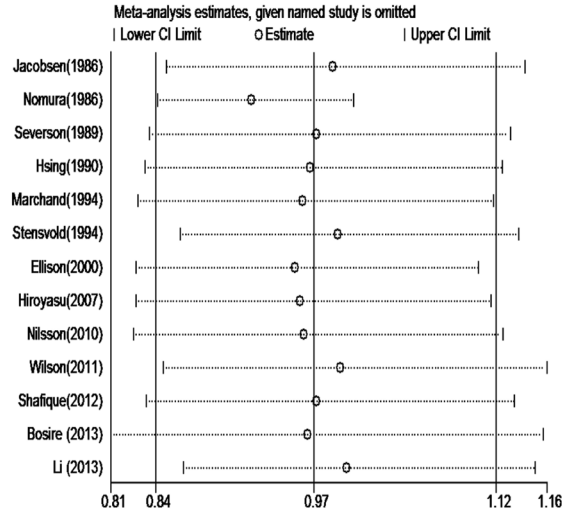

Figure 3. The sensitivity analysis diagram for each study used to assess the relative risk estimates for coffee consumption and prostate cancer risk in the cohort studies.

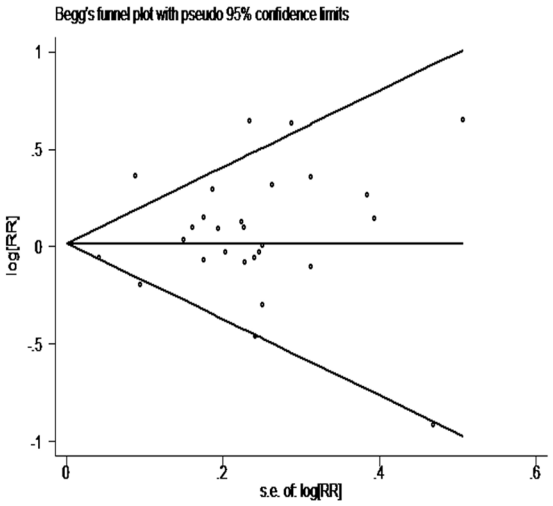

Figure 4. Publication bias in all the studies. Both visualization of funnel plot and Begg's test (P = .632), or Egger's test (P = .229) test indicated no publication bias in the studies included in the meta-analysis.

studies, we found an apparent difference between them ((hospital based RR: 1.50 (95% CI: 1.21-1.85, P < .001); population-based RR was 1.06 (95% CI: 0.91-1.23, P = .445)). Based on different geographic regions, the summary RRs were 1.06 (95% CI: 0.86-1.30, P = .586) for the studies conducted in Europe, 1.06 (95% CI: 0.93-1.20, P = .361) for the studies performed in America, and 1.12 (95% CI: 0.70-1.79, P = .635) for the studies carried out in Asia. According to the quality of studies, the pooled RRs for high quality and low quality were respectively 1.15 (95% CI: 0.99-1.34, P = .060), 1.28 (95% CI: 1.03-1.58, P = .026) in the case-control studies; and respectively 1.02 (95% CI: 0.88-1.20, P = .781), 0.81 (95% CI: 0.57-1.14, P = .221) in the cohort studies. Based on the studies, which explored the relationship of CC with stage-specific PC, the meta-analysis showed that the pooled RRs were 0.90 (95% CI: 0.69-1.16, P = .399) in the advanced PC, but 0.90 (95% CI: 0.84-0.97, P = .006) in the localized PC.

There was some evidence of heterogeneity among all the studies of CC overall (P = .001, I2 = 52.2%), and the heterogeneity mainly existed in the cohort studies (P = .001, I2 = 64.8%). As the heterogeneity was remarkable, we conducted a sensitivity analysis with any single study omitted in all the studies. The results showed that the pooled RRs and 95% CI changed little, which indicated that the meta-analysis results were stable (**Figure 3**). To explore the source of heterogeneity among the cohort studies, we did the subgroup analysis by characteristics of studies. When stratified by study geographic area and methodological quality of study, the heterogeneity of the cohort studies reduced slightly but not significantly (**Table 2**).

Dose-response meta-analysis

We incorporated nineteen studies (nine case-control studies[12,18,19,22,33-37] and ten cohort studies[13,15-17,20,21,42,44,46,47] into the dose-response analysis of CC and risk of PC (**Table 2**), because other remaining studies reported only 2 quantitative exposure categories [38,40], or did not provide cutoff of coffee intake in each category [32,39,41,44], or did not reveal the number of cases and non-cases in each exposure category[41,43]. There was marginally statically significant departure from linearity (P = .049). The pooled RR for a one cup per day increment in CC was 0.99 (95% CI: 0.98-1.00), which was evident for cohort studies (RR = 0.99, 95% CI: 0.98-1.00, P = .012) , but not significant in the case-control studies (RR = 1.01, 95% CI: 0.95-1.06, P = .825). When grouped by stage-specific prostate cancer, the pooled RR for studies conducted in localized PC was 0.98 (95% CI: 0.98-0.99, P = .003), but 0.98 (95% CI: 0.94-1.02, P = .410) in advanced PC.

Publication bias

No evidence of publication bias was found from either visualization of funnel plot, Begg's test (P = .632), or Egger's test (P = .229) (**Figure 4**). There was no significant indication of publication bias for the sixteen studies, which were included in the dose-response analysis (Begg's P = .629; Egger's P = .152).

DISCUSSION

Based on the published results from 14 case-control and 14 cohort studies, our meta-analysis assessed the potential association between CC and PC. The overall pooled RR of PC for high versus non/lowest coffee consumption was 1.07 (95% CI: 0.96-1.18), which indicates that CC is not associated with an increased risk of PC. Stratified by study design, the meta-analysis showed CC increased the risk of PC in the case-control studies, but did not increase in the cohort studies. The discrepancy of the results between case-control and cohort studies may be explained with potential biases of case-control studies, such as selection bias and recall bias. Additionally, it is worth noting that when subgrouped by the control characteristics or quality of case-control studies, there was not an increased risk of PC in population-based or high quality of case-control studies despite its presence in hospital-based and low quality of case-control studies. Generally, population-based case-control studies are considered more reliable because their subjects are more representative as controls than those of hos-

pital-based case-control studies. As we know, the design and methodology of studies could affect the efficacy outcome differently. Hence, these results above suggested that there is no causal relationship between coffee drinking and increased PC. On the contrary, the dose-response relationship analysis showed that there was an inverse dose-response relationship between a one cup per day increment and decreased risk of PC (P = .049), which was more significant in cohort studies (P = .012). More interestingly, in the subgroup of stage-specific PC of both high versus non/lowest CC and dose-response meta-analysis, we found that CC could substantially reduce the localized, rather than advanced prostate cancer incidence. Therefore, based on the results of our analyses, we could conclude that CC could not increase the incidence of PC, but reduce the risk of localized prostate cancer.

Compared with the previous meta-analyses, our meta-analysis has some advantages. Firstly, it is well known that the inclusiveness of all relevant studies for the meta-analyses is very important. In Park et al. ' meta-analysis (8), they totally included twelve studies (eight case-control studies and four cohort studies) and found RR of 1.16 (95% CI: 1.01–1.33) for highest versus lowest coffee drinkers. In another one, it only contained five prospective cohort studies and shows an inverse association of PC risk with high coffee intake (RR 0.79, 95% CI: 0.61–0.98)[9]. Recently, there is another meat-analysis demonstrating a borderline significant inverse association between CC and PC risk based on cohort studies. Altogether, these results are inconsistent and confusing. We include all the published studies available as possible as we could, and the number of total cases included in the meta-analysis was more massive (14 case-control and 14 cohort studies). Secondly, because cutoffs for the highest coffee categories varied from each study, the dose–response relationship analysis is especially important. The dose–response relationship is to describe the change in effect on an organism caused by differing levels of exposure (or doses) to a stressor after a certain exposure time, and it is critical for determining "safe" and "hazardous" levels and dosages for drugs, potential pollutants, and other substances to which humans or other organisms are exposed[48]. We did a dose-response meta-analysis, which was not carried out specially in either of the previous meta-analyses. Thirdly, as we know, publication bias is much of concern in a meta-analysis, and there was little evidence of publication bias in our meta-analysis. Finally and the most importantly, to the best of our knowledge, in the meta-analysis, we first evaluate subgroups based on the stage of PC, finding that there is an inverse association with the incidence of localized rather than advanced PC.

Coffee is produced by infusing ground, roasted coffee beans, with the most common forms being coffea arabica and coffea canephoria var. robusta[49]. Coffee contains more than a thousand different chemicals. While it has caffeine and methylglyoxal with potentially carcinogenic effects, some other chemicals have been suggested to have potentially chemo-preventive effects, such as chlorogenic, caffeic acids, diterpenes cafestol and kahweol[7,50-52]. Our analyses have found that coffee drinking could reduce the risk of localized but not advanced PC. This is an investing finding. It has been reported that other environmental agents, like chemical, physical or microbial agents, could enhance or suppress coffee on the carcinogenic effect, depending on the carcinogen it is used with, the type of host cell, and the stage of cell cycle in which it is introduced[53]. It is hypothesized that coffee drinking may be associated with increased levels of sex hormone-binding globulin (SHBG) and total testosterone levels, which might play a role in PC[54]. However, a recent randomized trial showed that consumption of caffeinated coffee had no evident effect on SHBG levels, but significantly increased total testosterone and decreased both total and free estradiol in men[55]. At the same time, CC is also associated with reductions in the levels of inflammation-related molecule, which have an important role in prostatic carcinogenesis[56]. Furthermore, an animal study showed that caffeine treatment increased the percentage of mitotic tumor cells undergoing lethal mitosis, which indicated oral administration of caffeine might be an effective strategy for the prevention of PC progression[57].

Despite these advantages, there are still some limitations. Firstly, heterogeneity among studies may have been involved because of methodological differences among studies, including different methods of coffee preparation, misclassification of CC, differences in serving size and brew strength. Furthermore, the individual RR estimate included in our meta-analysis was adjusted for different covariates in the different studies. Nevertheless, the results did not change substantially after the sensitivity analysis. Secondly, unfortunately, because of the small number of studies investigating the relationship between CC and subtypes of PC, our meta-analysis could only evaluate subgroups based on tumor stage, but not on Gleason grade or prostate cancer-specific mortality. Lastly, most of the studies in this meta-analysis were conducted in Europe, the United States, Canada and Japan; thus the data should be extrapolated to other populations with caution.

CONCLUSIONS

In summary, although data from low quality case-control studies suggest that coffee is a risk factor for PC, there is no association between CC and increased PC based on the results of high quality of case-control studies and cohort studies and dose-response analysis. On the contrary, according to the stage-specific prostate cancer, subgroups analysis showed that CC could be a protective exposure that reduces the localized PC risk. However, prospective studies, focusing on more detailed results, including subtypes of coffee, taking a broad range of confounders into account, are required to clarify this relationship.

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CONFLICT OF INTEREST

The authors have no conflict of interest.

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