Alcohol consumption and incidence of prostate cancer among Chinese people: A systematic review and meta-analysis

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Abstract

Aims: Meta-analyses have suggested a dose-response relationship between level of alcohol use and risk of prostate cancer, but the populations in the included studies are predominantly Caucasian. Many Chinese language studies have not been included in published reviews and/or meta-analyses. The present meta–analysis accessed research reports in both English and Chinese language sources in order to investigate this relationship specifically among Chinese people.

Methods: Searches in five large Chinese biomedical bibliographic databases were made for case–control and cohort studies of alcohol consumption and prostate cancer incidence and death (ICD–10: C61) up to May 2017. Studies were coded for design, outcome, drinker and non-drinkers, extent of control for confounding and other study characteristics. Mixed models were used to estimate relative risk (RR) of incidence or death from prostate cancer due to alcohol consumption with study level controls for designs, drinker bias and types of drinkers.

Findings: A total of 415 studies were identified of which 25 (20 in Chinese from five Chinese databases and 5 in English from published meta-analyses) satisfied inclusion criteria providing 36 risk estimates of prostate cancer for drinkers versus non-drinkers. There was a total of 36 OR estimates; 27 using patients as controls and 9 using healthy people. Nine studies (14 OR estimates) specified reference abstainers as "never drank" or "no drinking". Adjusted RR estimates indicated a significantly increased risk of prostate cancer among drinkers (RR=1.46, 95% CI: 1.40 – 1.52, t-test P<0.001) compared to non-drinkers. Dose-response relationships (t-test P<0.001) were evident in three studies that assessed level of alcohol intake.

Conclusions: There is a significantly higher risk of prostate cancer incidence among Chinese drinkers than non-drinkers, with some evidence of a dose-response relationship. However, almost all the identified studies suffered from former and/or occasional drinker biases. Few studies had adequate measures of level of alcohol intake and further well-designed studies are required.

Prostate cancer is the development of cancer in the prostate, a walnut–sized gland in men that surrounds the top of the urethra and which produces seminal fluid (Bostwick, Crawford, Higano, & Roach, 2004). Its growth and functions are controlled by male hormones such as testosterone. Prostate cancer is the second most common cancer in men worldwide. Around 1.1 million cases were recorded in 2012, accounting for 15% of all new cases of cancer in men (Forman & Ferlay, 2014). It is the fifth most common cause of cancer death in men worldwide. There have been marked geographic, racial and ethnic variations in incidence and mortality of prostate cancer variously due to under-diagnosis, underreporting, differences in screening practices, differences in health-care access, gaps in knowledge and awareness and prevalence level of risk factors such as alcohol consumption (Hsing & Devesa, 2001; Taitt, 2018). It is most commonly diagnosed in high–income western countries, where screening is common. However, the incidence of prostate cancer appears to be increasing in Asian countries such as Japan and China even though prostate-specific antigen (PSA) testing is not often used (Baade, Youlden, & Krnjacki, 2009). It has been recognized

that prostate cancer is a currently common disease among Chinese males. The incidence rate was about 9.8 per 100,000 males in 2014, a significantly increased trend since 2008 (National Health Commission of the People's Republic of China, 2019; Ye & Zhu, 2015). Therefore, prostate cancer as a chronic disease has become an important public health concern in developing countries such as China.

The risk factors for prostate cancer that can be considered established include age, race/ethnicity and family history (Gann, 2002). Many observational studies conducted mainly in Caucasian populations have investigated alcohol consumption as a risk factor for prostate cancer. Conclusions from these studies and of reviews have been conflicting with some finding increased risk of prostate cancer (Hayes et al., 1996; Sesso, Paffenbarger, & Lee, 2001; Watters, Park, Hollenbeck, Schatzkin, & Albanes, 2010), or decreased risk (Dagnelie, Schuurman, Goldbohm, & Van den Brandt, 2004) and others finding no relationship (Hiatt, Armstrong, Klatsky, & Sidney, 1994; Longnecker, 1995; Morton, Griffiths, & Blacklock, 1996; Stemmermann, Nomura, Chyou, & Yoshizawa, 1990; Tavani, Negri, Franceschi, Talamini, & Lavecchia, 1994; Vandergulden, Verbeek, & Kolk, 1994). Over the past few decades there have been several reviews and meta–analyses conducted to examine the association of prostate cancer with alcohol consumption (Bagnardi, Blangiardo, La Vecchia, & Corrao, 2001; Breslow & Weed, 1998; Dagnelie et al., 2004; Dennis, 2000; Fillmore, Chikritzhs, Stockwell, Bostrom, & Pascal, 2009; Li, Yang, & Cao, 2011; Longnecker, 1995; Morton et al., 1996; Rota et al., 2012; Zhao, Stockwell, Roemer, & Chikritzhs, 2016) because of inconsistent results regarding the relationship between prostate cancer and alcohol consumption across individual studies. The most recent one, mainly based on the studies conducted in western countries shows a significant dose-response relationship (Zhao et al., 2016).

Because prior reviews and/or meta-analyses were conducted based on the studies searched and analyzed in English journals from English databases, these studies were mainly conducted with Caucasian populations. These published reviews and/or meta-analyses included few studies conducted in non-Caucasian populations such as Asians. Few studies conducted in Asian populations have been published in English journals and thus included in published reviews and meta-analyses. Over years, only six studies conducted on the Chinese population in China were included in published reviews and meta-analyses and one of these six studies was published in a Chinese journal (Breslow & Weed, 1998; Dennis, 2000; Wei, Tang, Yang, Zhan, & Yin, 1994) and other five in English journals (Hsing et al., 1994; Jian, Xie, Lee, & Binns, 2004; Lee et al., 1998; Li et al., 2008; Yang et al., 2006). Meta-analysis by Li et al. (2011) included only four case-control studies of prostate cancer and alcohol consumption and found no relationship (Li et al., 2011). Among these six reviewed studies (nine risk estimates) in Chinese populations living in mainland China, only one shows a significantly increased risk when healthy people were treated as controls (Hsing et al., 1994). No studies were conducted on Chinese populations in other countries or regions. It is unclear whether or not those

studies published in Chinese journals or non-English journals that cannot be located in English databases show different results as the risk estimates in published meta-analyses. Biological studies suggested that the effects of alcohol use on incidence of prostate cancer differed by race and/or environment because encoded enzymes involved in metabolizing alcohol differ by race. Alcohol is metabolized in the body mainly by the liver. Most of the ethanol in the body is broken down in the liver by an enzyme called alcohol dehydrogenase (ADH) which transforms ethanol into a toxic compound called acetaldehyde, a known carcinogen (Edenberg, 2007). Acetaldehyde is quickly broken down to a less toxic compound called acetate (Edenberg, 2007) by another enzyme called acetate dehydrogenase (ALDH). Acetate is then broken down to carbon dioxide and water for easy elimination (Edenberg, 2007). A person's risk of alcohol-related cancers is influenced by their genes that encode enzymes involved in metabolizing alcohol (Druesne-Pecollo et al., 2009). Many East Asian people carry a version of the gene for ADH that codes for a "superactive" form of the enzyme. This superactive ADH enzyme speeds the conversion of alcohol to toxic acetaldehyde. Among people of Japanese descent, those who have this form of ADH have a higher risk of pancreatic cancer than those with the more common form of ADH (Kanda et al., 2009). Research finds that genes encoding enzymes such as ADH1B involved in alcohol metabolism are polymorphic and that the superactive ADH1B*2 allele is highly prevalent (54-96%) among East Asians (Goedde et al., 1992) but relatively rare among Caucasians (1-23%). The less active ADH1B*1 is a risk factor for alcoholism in both Asians and Caucasians (Zintzaras, 2006; Zintzaras, Stefanidis, Santos, & Vidal, 2006). Some people of East Asian descent carry a variant of the gene for ALDH2 that encodes a defective form of the enzyme. In people who produce the defective enzyme, acetaldehyde builds up when they drink alcohol. The accumulation of acetaldehyde has such unpleasant effects that most people who have inherited the ALDH2 variant are unable to consume large amounts of alcohol and therefore have a low risk of developing alcohol-related cancers such as prostate cancer. Genetic differences in these enzymes suggest that the effect of alcohol consumption on prostate cancer maybe different among Asians such as Chinese from that found among Caucasians and it is thus necessary to investigate the relationship between prostate cancer and alcohol consumption in non-Caucasians, for instance in Chinese populations.

There has been a marked increase in the numbers of cancers diagnosed in China between 2000 and 2011 (Chen et al., 2016). Much of this is explained by the aging and growth of the population. Other factors that may have contributed to the increase in the burden of cancer include increases in the prevalence of unhealthy behaviors or cancer-related lifestyle and improvements in disease awareness, detection services, and data completeness. The largest increase in incidence was seen for cancers of the prostate for men and cervix and thyroid for women. The factors driving the increase in prostate cancer are not entirely understood. However, they may include gradual implementation of PSA screening and improved biopsy techniques (Ito, 2014) or the impact of an increasingly westernized lifestyle including alcohol

consumption (Baade, Youlden, Cramb, Dunn, & Gardiner, 2013; Baade et al., 2009). China has a large population that accounts for approximately 20% of world population (United Nations Department of Economic and Social Affairs Population Division, 2017) and thus the increasing number of prostate cancer cases is a significant and growing proportion of the total globally. There has not been large-scale screening for prostate cancer diagnosis in China (National Health Commission of the People's Republic of China, 2019). Alcohol consumption as a risk factor of many cancers has been increasing in China over years; per capita ethanol per male adult aged 15+ increased to 11.19 litres in 2017 from 7.08 in 1990 and 11.00 in 2010 (Manthey et al., 2019). The objective of the present meta-analysis was to investigate the relationship between prostate cancer and alcohol consumption among Chinese people.

Methods

Inclusion and exclusion criteria

The criteria for inclusion were: (i) case-control and cohort studies evaluating the relationship between alcohol consumption and incidence or death from prostate cancer; (ii) original articles published in Chinese Journals (Mandarin) or English Journals (English) up till April 2017; (iii) articles that reported findings as an odds ratio, hazard ratio, incidence ratio or standardized mortality ratio; (iv) studies conducted among Chinese people living in Mainland China; (v) articles reporting at any levels of alcohol consumption with drinking amounts, including the reference level; and (vi) studies reporting total alcohol consumption were included while studies based on consumption of specific beverages only such as wine, whiskey, vodka, sake or hard liquors were excluded. When the results of the study were published more than once or if the same dataset was used multiple times, only the most recent or more complete data were included in analyses. When published studies and dissertations were based on the same studies, the published articles were included in the analysis. When published studies used the data from the same studies, the studies that used the large samples were included. The primary outcomes of interest were mortality and/or morbidity from prostate cancer (ICD-9: 185 or ICD-10: C61) (WHO, 2010).

Search strategy

The systematic review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher, Liberati, Tetzlaff, Altman, & the PRISMA Group, 2009). The study identified all potentially relevant articles published in Chinese Journals by searching five large Chinese biomedical bibliographic databases including China National Knowledge Infrastructure (CHKD-CNKI), Chinese Medical Current Content (CMCC), Chinese Biomedical Literature Database (CBM), VIP information/Chinese Scientific Journal Database (csjd-vip,VIP database) and Wan-Fang Database/Chinese Medicine Premier. The combined five databases cover all studies conducted in China and published in Mandarin journals (Xia, Wright, & Adams, 2008). The relevant articles

were also searched through reference list cross-checking including those of previous meta-analyses (mainly English articles) and incorporating publications up to April 31, 2017. Hand searches of cited references in the selected articles, reviews and meta-analysis published on the same topic were also performed. The following MESH terms and text words were used: ("prostatic neoplasms" OR ("prostate" AND "neoplasms") OR "prostate cancer "OR ("prostate" AND "Cancer")) AND ("alcohol" OR (alcohol drinking) OR "alcohol consumption" OR "alcohol intake" OR ("alcohol" AND "consumption")).

Study selection

Two reviewers (DG, YL) read the titles and/or abstracts of all the citations retrieved from the electronic database searches and removed all citations that were clearly not related to studies of the relationship between prostate cancer and alcohol consumption. Full-text articles that met eligibility criteria were obtained for data collection. Two of the authors (DG, YL) independently evaluated all studies selected for inclusion. The initial search identified a total of 415 studies of which 21 studies (Dong et al., 2016; Jia et al., 2013; Liang, Liu, Zhou, Gao, & Chen, 2007; Liu, Wang, Gu, & Zhou, 2014; Liu, J. et al., 2014; Lu, Hua, & Wang, 2011; Ma, 2014; Min, Mi, Shao, Feng, & Hua, 2012; Shao et al., 2012; Wang et al., 2014; Wei, Bin, & Huang, 2017; Wei et al., 1994; Wu, Xu, & Li, 2010; Wu, 2011; Wu, 2008; Xu, 2010; Xu et al., 2007; Yang, 2006; Zhang, Qiu, Shi, Liu, & Chou, 1999; Zhang, Liang, & Cui, 2012; Zhang et al., 2011) satisfied the criteria for the meta-analysis after removing 394 records for reasons identified in Figure 1. In addition we also included seven risk estimates from five studies (four published in English and one in Chinese journal) included in previously published reviews and meta-analyses (Hsing et al., 1994; Jian et al., 2004; Lee et al., 1998; Li et al., 2008; Yang et al., 2006). The study by Yang et al. (2006) published in an English journal is the same study as the thesis by Yang (2006) and the article by Yang et al (2009) (Li et al., 2011; Yang et al., 2009). Our study thus includes the study published in English journal because of the large sample size of cases. This meta-analysis includes 25 original studies in which 36 ORs are presented. All 25 included studies are case-control studies which examined the relationship between incidence of newly-diagnosed prostate cancer and alcohol consumption. No cohort studies on the topic conducted in Chinese population were identified.

Data extraction

Two reviewers (DG, YL) independently reviewed all eligible papers to extract and code data from all studies fulfilling the inclusion criteria, and any disagreements were resolved by discussion. Where disagreements existed, both reviewers discussed the discrepancy until a consensus was reached. Each study was coded with reference to a standardized code-book created and used in several published meta-analyses (Stockwell et al., 2016; Zhao et al., 2016; Zhao, Stockwell, Roemer, Naimi, & Chikritzhs, 2017) (available from authors on request). The coding of all variables in the meta-dataset was double-checked by two other authors (JZ, TS). The data to be extracted were: (1)

outcome, mortality or morbidity of prostate cancer and risk estimates; (2) types of study design and types of control used in case-control studies; (3) measures of alcohol consumption; (4) study characteristics; and (5) controlled variables in individual studies.

Figure 1

Flow diagram of systematic review of studies examining the relationship between alcohol consumption and prostate cancer among Chinese people
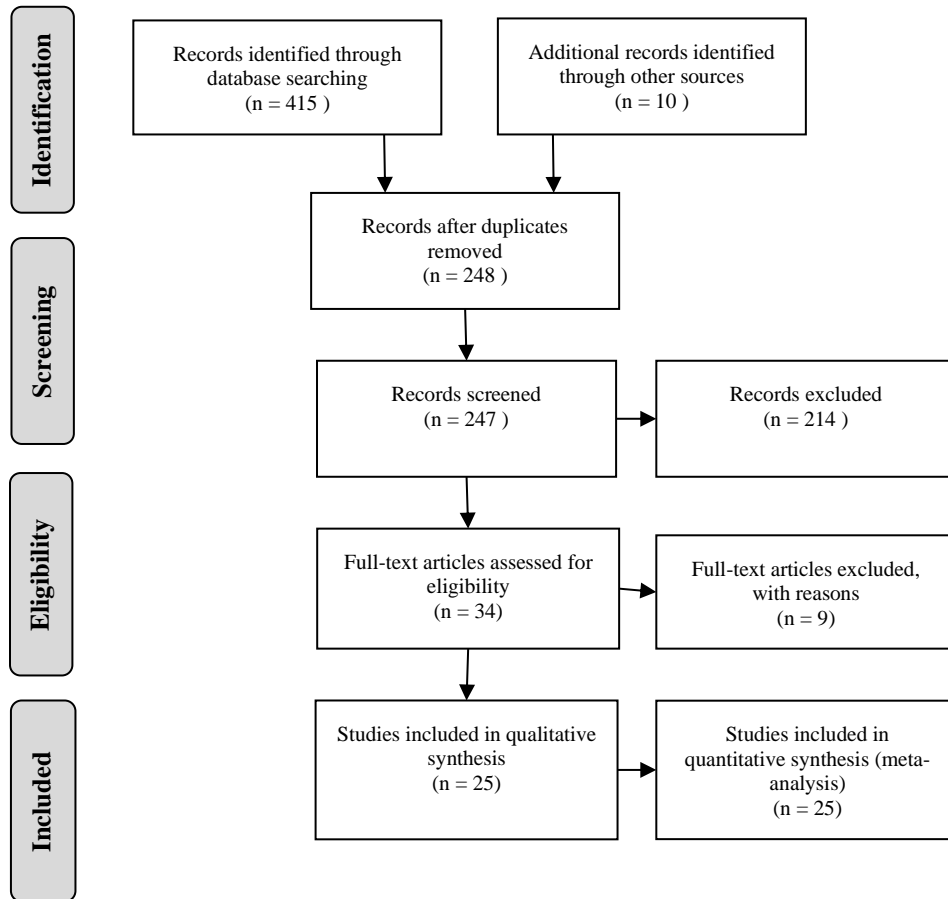
The study used various controls (shown in Table 1) and we examined the effect of types of control. These included studies defined "drinkers" and "non-drinkers" variously (shown in Table 2). No studies investigated the dose-response relationship of prostate cancer and alcohol consumption and thus we coded definitions of alcohol drinkers and non-drinkers in each study and assessed whether former and occasional or light drinkers were misclassified into the reference group consisting of lifetime non-drinkers.

Strategy for data analysis

All included studies used case-control designs and thus the odds ratio (OR) estimates in case-control studies were entered as observations of the estimated risk relationships for meta-analysis. Mixed effects models were used to obtain the summarized risk estimates (Woodward, 2000).

In mixed multivariate meta-regression analysis, the dependent variable was the natural log of the RR estimated using the ORs of prostate cancer for drinkers and non-drinkers. Sensitivity analyses were run after excluding the studies by one by one and excluding the studies published in English journals and included in previously published meta-analyses. An analysis on dose-response relationship was performed. More details of statistical analysis strategy can be found in Appendix I. All significance tests assumed two–tailed P values or 95% CIs. All statistical analyses were performed using SAS 9.4.

Table 1

25 case-controlled studies with 36 odds ratio (OR) estimates and the corresponding 95% confidence interval (CI) selected for analysis of the association of incidence of prostate cancer with alcohol consumption among Chinese people, 1994–2017
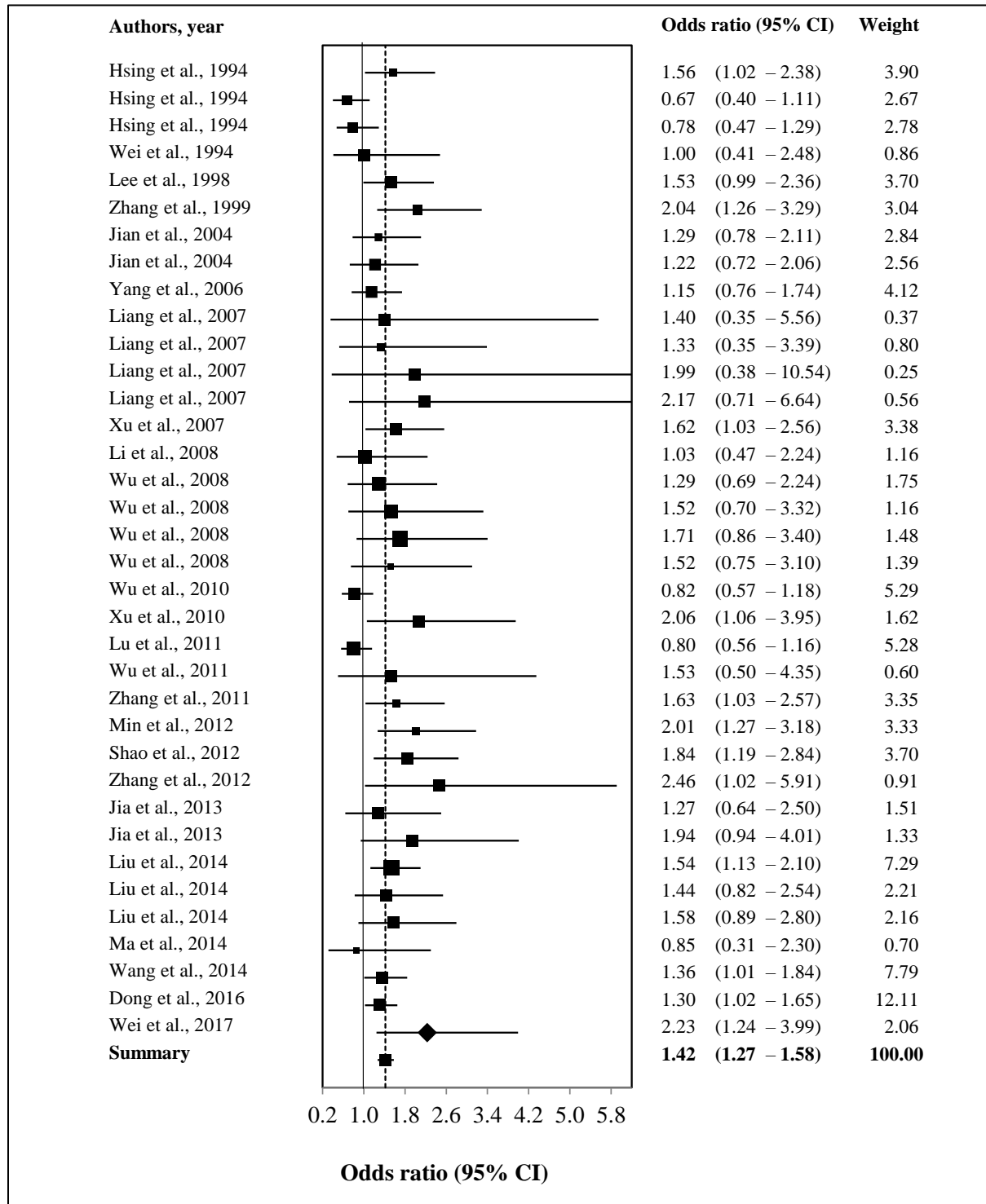
Author	Pub year	No. of cases	No of controls	Mean age	Control †	OR (95% CI)	Covariate assessed ‡
Hsing et al.	1994	135	314	68.93	5	1.56 (1.02 – 2.38)	1, 2, 3
Hsing et al.	1994	135	158	68.93	1	0.67 (0.40 – 1.11)	1, 2, 3
Hsing et al.	1994	135	157	69.08	3	0.78 (0.47 – 1.29)	1, 2, 3
Wei et al.	1994	27	54		3	1.00 (0.41 – 2.40)	1, 2, 3, 4
Lee et al.	1998	133	265	69.50	1	1.53 (0.99 – 2.36)	1, 2, 3, 4
Zhang et al.	1999	137	137	69.39	7	2.04 (1.26 – 3.29)	1, 2, 3
Jian et al.	2004	88	212	71.87	5	1.29 (0.78 – 2.11)	1, 2, 3, 4
Jian et al.	2004	92	204	71.87	5	1.22 (0.72 – 2.06)	1, 2, 3
Yang et al.	2006	225	250	71.28	4	1.15 (0.76 – 1.74)	1, 2, 3
Liang et al.	2007	50	58	69.32	2	1.40 (0.35 – 5.56)	1, 2, 3, 4
Liang et al.	2007	56	57	69.32	7	1.33 (0.52 – 3.39)	1, 2, 3, 4
Liang et al.	2007	50	56	69.32	2	1.99 (0.38 –10.54)	1, 2, 3, 4
Liang et al.	2007	56	57	69.32	7	2.17 (0.71 – 6.64)	1, 2, 3, 4
Xu et al.	2007	207	235	71.20	5	1.62 (1.03 – 2.56)	1, 2, 3
Li et al.	2008	28	280	68.00	1	1.03 (0.47 – 2.24)	1, 2, 3, 4
Wu et al.	2008	121	127	70.86	2	1.29 (0.69 – 2.43)	1, 2, 3, 4
Wu et al.	2008	117	121	70.86	7	1.53 (0.70 – 3.32)	1, 2, 3, 4
Wu et al.	2008	121	126	70.86	2	1.71 (0.86 – 3.40)	1, 2, 3, 4
Wu et al.	2008	117	125	70.86	7	1.53 (0.75 – 3.10)	1, 2, 3, 4
Wu et al.	2010	209	268	71.56	5	0.82 (0.57 – 1.18)	1, 2, 3
Xu et al.	2010	141	282	71.11	5	2.06 (1.06 – 3.95)	1, 2, 3
Lu et al.	2011	200	279	71.56	1	0.80 (0.56 – 1.16)	1, 2, 3, 4
Wu et al.	2011	434	1,531	74.88	1	1.53 (0.50 – 4.35)	1, 2, 3, 4
Zhang et al.	2011	108	242	70.01	1	1.63 (1.03 – 2.57)	1, 2, 3, 4
Min et al.	2012	168	208	69.00	1	2.01 (1.27 – 3.18)	1, 2, 3, 4
Shao et al.	2012	174	252	73.77	1	1.84 (1.19 – 2.84)	1, 2, 3, 4
Zhang et al.	2012	60	40	75.85	2	2.46 (1.02 – 5.91)	1, 2, 3, 4
Jia et al.	2013	86	86	72.22	2	1.27 (0.64 – 2.50)	1, 2, 3, 4
Jia et al.	2013	86	86	72.22	7	1.94 (0.94 – 4.01)	1, 2, 3, 4
Liu et al.	2014	267	534	70.84	2	1.54 (1.13 – 2.10)	1, 2, 3, 4
Liu et al.	2014	120	120	73.12	7	1.44 (0.82 – 2.54)	1, 2, 3, 4
Liu et al.	2014	120	120	73.12	2	1.58 (0.89 – 2.80)	1, 2, 3, 4
Ma et al.	2014	103	100	71.20	5	0.85 (0.31 – 2.30)	1, 2, 3
Wang et al.	2014	410	440	71.40	1	1.36 (1.01 – 1.84)	1, 2, 3
Dong et al.	2016	664	702	71.50	6	1.30 (1.02 – 1.65)	1, 2, 3, 4
Wei et al.	2017	128	128	71.56	5	2.23 (1.24 – 3.99)	1, 2, 3

†1=healthy people; 2=benign prostatic hyperplasia; 3=other cancer; 4=other urological disease; 5=patients without cancer, 6=patients without prostate cancer, 7=patients without prostate disease.

‡Controlled confounders: 1=age; 2=race; 3=residence; 4=smoker.

Figure 2

36 odds ratio (95% CI) estimates of prostate cancer incidence for any alcohol consumption versus abstaining in 25 Chinese case-controlled studies

Authors, year	Odds ratio (95% CI)	Weight
Hsing et al., 1994	1.56 (1.02 − 2.38)	3.90
Hsing et al., 1994	0.67 (0.40 − 1.11)	2.67
Hsing et al., 1994	0.78 (0.47 − 1.29)	2.78
Wei et al., 1994	1.00 (0.41 − 2.48)	0.86
Lee et al., 1998	1.53 (0.99 − 2.36)	3.70
Zhang et al., 1999	2.04 (1.26 − 3.29)	3.04
Jian et al., 2004	1.29 (0.78 − 2.11)	2.84
Jian et al., 2004	1.22 (0.72 − 2.06)	2.56
Yang et al., 2006	1.15 (0.76 − 1.74)	4.12
Liang et al., 2007	1.40 (0.35 − 5.56)	0.37
Liang et al., 2007	1.33 (0.35 − 3.39)	0.80
Liang et al., 2007	1.99 (0.38 − 10.54)	0.25
Liang et al., 2007	2.17 (0.71 − 6.64)	0.56
Xu et al., 2007	1.62 (1.03 − 2.56)	3.38
Li et al., 2008	1.03 (0.47 − 2.24)	1.16
Wu et al., 2008	1.29 (0.69 − 2.24)	1.75
Wu et al., 2008	1.52 (0.70 − 3.32)	1.16
Wu et al., 2008	1.71 (0.86 − 3.40)	1.48
Wu et al., 2008	1.52 (0.75 − 3.10)	1.39
Wu et al., 2010	0.82 (0.57 − 1.18)	5.29
Xu et al., 2010	2.06 (1.06 − 3.95)	1.62
Lu et al., 2011	0.80 (0.56 − 1.16)	5.28
Wu et al., 2011	1.53 (0.50 − 4.35)	0.60
Zhang et al., 2011	1.63 (1.03 − 2.57)	3.35
Min et al., 2012	2.01 (1.27 − 3.18)	3.33
Shao et al., 2012	1.84 (1.19 − 2.84)	3.70
Zhang et al., 2012	2.46 (1.02 − 5.91)	0.91
Jia et al., 2013	1.27 (0.64 − 2.50)	1.51
Jia et al., 2013	1.94 (0.94 − 4.01)	1.33
Liu et al., 2014	1.54 (1.13 − 2.10)	7.29
Liu et al., 2014	1.44 (0.82 − 2.54)	2.21
Liu et al., 2014	1.58 (0.89 − 2.80)	2.16
Ma et al., 2014	0.85 (0.31 − 2.30)	0.70
Wang et al., 2014	1.36 (1.01 − 1.84)	7.79
Dong et al., 2016	1.30 (1.02 − 1.65)	12.11
Wei et al., 2017	2.23 (1.24 − 3.99)	2.06
Summary	**1.42 (1.27 − 1.58)**	**100.00**

0.2 1.0 1.8 2.6 3.4 4.2 5.0 5.8

Odds ratio (95% CI)

Results

There were 25 case-control studies identified spanning the years 1994–2017 that examined the relationship between prostate cancer incidence and alcohol consumption; four of them are dissertations in Chinese (Ma, 2014; Wu, 2011; Wu, 2008; Xu, 2010) and 16 studies were published in Chinese journals (Dong et al., 2016; Jia et al., 2013; Liang et al., 2007; Liu,C. et al., 2014; Liu, J. et al., 2014; Lu et al., 2011; Min et al.,2012; Shao et al., 2012; Wang et al., 2014; Wei et al., 2017; Wei et al., 1994; Wu et al., 2010; Xu et al., 2007; Zhang et al., 1999; Zhang et al., 2012; Zhang et al., 2011) and five (Hsing et al., 1994; Jian et al., 2004; Lee et al., 1998; Li et al., 2008; Yang et al., 2006) in English journals. Table 1 presents the basic characteristics of these studies including controlled covariates included in individual studies. As shown in Table 1, there were 36 risk estimates available for alcohol exposures across the 25

selected studies. These studies used 4,488 patients with diagnosis of incidence of prostate cancer as cases but different controls (a total of 7,830 controls) and defined the exposures differently. Eight OR estimates used hospital patients with diagnosis of benign prostatic hyperplasia as controls (Jia et al., 2013; Liang et al., 2007; Liu, C. et al., 2014; Liu, J. et al., 2014; Wu, 2008; Zhang et al., 2012), nine healthy subjects (Hsing et al., 1994; Lee et al., 1998; Li et al., 2008; Lu et al., 2011; Min et al., 2012; Shao et al., 2012; Wang et al., 2014; Wu, 2011; Zhang et al., 2011), 16 patients without a diagnosis of cancer (Hsing et al., 1994; Jian et al., 2004; Ma, 2014; Wei et al., 2017; Wu et al., 2010; Xu et al., 2007) or prostate cancer (Dong et al., 2016) or prostate disease (Jia et al., 2013; Liang et al., 2007; Liu, C. et al., 2014; Liu, J. et al., 2014; Wu, 2008; Zhang et al., 1999), and three patients with other cancer (Hsing et al., 1994) or other cancers (Wei et al., 1994) or other urological diseases (Yang et al., 2006).

Table 2

Definition of non-drinkers and drinkers in 25 Chinese case-controlled studies on alcohol use and prostate cancers

Author	Pub year	OR (95% CI)	Definition of abstainer reference	Definition of alcohol drinkers
Hsing et al.	1994	1.56 (1.02 – 2.38)	Never alcohol use	Ever alcohol use
Hsing et al.	1994	0.67 (0.40 – 1.11)	Never alcohol use	Ever alcohol use
Hsing et al.	1994	0.78 (0.47 – 1.29)	Never alcohol use	Ever alcohol use
Wei et al.	1994	1.00 (0.41 – 2.40)	No drink	Drink
Lee et al.	1998	1.53 (0.99 – 2.36)	Never used alcohol	Ever used alcohol
Zhang et al.	1999	2.04 (1.26 – 3.29)	No drink	Drink
Jian et al.	2004	1.29 (0.78 – 2.11)	Never drank	>0-25drinks (1D=15g) weekly
Jian et al.	2004	1.22 (0.72 – 2.06)	Never drank	>25 drinks (1 D=15g) weekly
Yang et al.	2006	1.15 (0.76 – 1.74)	<3 times weekly for 10+ years	3+ times weekly for 10+ years
Liang et al.	2007	1.40 (0.35 – 5.56)	<1g per day	1 – 100 g per day
Liang et al.	2007	1.33 (0.52 – 3.39)	<1g per day	>100 g per day
Liang et al.	2007	1.99 (0.38 –10.54)	<1g per day	1 – 100 g per day
Liang et al.	2007	2.17 (0.71 – 6.64)	<1g per day	>100 g per day
Xu et al.	2007	1.62 (1.03 – 2.56)	<3 times weekly for 10+ years	3+ times weekly for 10+ years
Li et al.	2008	1.03 (0.47 – 2.24)	Never drank	Ever drink
Wu et al.	2008	1.29 (0.69 – 2.43)	<1g per day	1 – 100 g per day
Wu et al.	2008	1.53 (0.70 – 3.32)	<1g per day	>100 g per day
Wu et al.	2008	1.71 (0.86 – 3.40)	<1g per day	1 – 100 g per day
Wu et al.	2008	1.53 (0.75 – 3.10)	<1g per day	>100 g per day
Wu et al.	2010	0.82 (0.57 – 1.18)	<3 times weekly for 10+ years	3+ times weekly for 10+ years
Xu et al.	2010	2.06 (1.06 – 3.95)	<1 time weekly for 6+ months	1+ time weekly for 6+ months
Lu et al.	2011	0.80 (0.56 – 1.16)	<3 times weekly for 10+ years	3+ times weekly for 10+ years
Wu et al.	2011	1.53 (0.50 – 4.35)	<1 time weekly for 6+ months	1+ time weekly for 6+ months
Zhang et al.	2011	1.63 (1.03 – 2.57)	<1 time weekly for 6+ months	1+ time weekly for 6+ months
Min et al.	2012	2.01 (1.27 – 3.18)	No drink	Drink
Shao et al.	2012	1.84 (1.19 – 2.84)	<3 times weekly for 10+ years	3+ times weekly for 10+ years
Zhang et al.	2012	2.46 (1.02 – 5.91)	<1 time weekly for 6+ months	1+ time weekly for 6+ months
Jia et al.	2013	1.27 (0.64 – 2.50)	<150 g per day	150+ g per day
Jia et al.	2013	1.94 (0.94 – 4.01)	<150 g per day	150+ g per day
Liu et al.	2014	1.54 (1.13 – 2.10)	Drink<1 year	Drink for 1+ year
Liu et al.	2014	1.44 (0.82 – 2.54)	No drink	Drink
Liu et al.	2014	1.58 (0.89 – 2.80)	No drink	Drink
Ma et al.	2014	0.85 (0.31 – 2.30)	Never drank	Ever drink
Wang et al.	2014	1.36 (1.01 – 1.84)	<3 times weekly for 6+months	3+ times weekly for 6+months
Dong et al.	2016	1.30 (1.02 – 1.65)	<3 times weekly for 6+months	3+ times weekly for 6+months
Wei et al.	2017	2.23 (1.24 – 3.99)	Never drank	Ever drink

Note: The descriptions of the abstainers and drinkers are directly translated from the original studies.

No studies examined dose-response relationship although three studies estimated ORs for two drinking categories (Jian et al., 2004; Liang et al., 2007; Wu, 2008). All these case-control studies presented the OR estimates of prostate cancer incidence for defined drinkers compared with defined non-drinkers. Defined drinkers are those who drank once a week for more than 6 months (4 OR estimates), at least 3 times a week for more than 6 months (2), at least 3 times a week for more than 10 years (5), drank for more than one year (2), 150+ g per day (2), drank 1-25 g per day (1) and >25 g per day (1), drank 1-100 g (4) and >100 g per day (4) and ever drank (11).

A forest plot (see Figure 2) displays the 36 OR estimates for the risk of prostate cancer associated with any level of drinking versus "abstaining" reported in individual studies. A visual inspection of Figure 2 indicates considerable cross-study variation in estimates. Among 36 OR estimates for any drinking versus non-drinking in 25 studies, 12 OR estimates are significantly higher than one, and 18 higher and five lower than one but not statistically significant, and one equal one. Mean OR is 1.42 (95% CI: 1.27 – 1.58, P<0.0001)

showing a significantly higher OR of prostate cancer among "drinkers" than "non-drinkers".

Table 3 presents unadjusted mean OR estimates of prostate cancer incidence overall and by study design (population-based and hospital-based controls), drinker bias (non-drinker reference groups were not defined as never drank), types of drinkers, and studies with and without controlled smoking status with tests of publication bias and heterogeneity. Compared to the "non-drinkers", being a drinker was associated with a significantly increased risk of prostate cancer overall and by subgroups. Figure 3 provides a funnel plot showing the log-ORs and their inverse standard error from which there was no marked indication of publication bias as the plot is reasonably symmetrical. No significant publication bias was detected using the Egger's regression either for the pooled data or studies with different controls, drinker bias and defined drinking (P>0.05 for each category). There was a significant heterogeneity detected using the Q statistic in either the pooled or some individual studies with different controls and defined drinking category estimates (P<0.01 in each case).

Figure 3

Funnel plot of relative risk (1n(OR)) of prostate cancer incidence due to alcohol consumption against inverse standard error of 1n(OR in 25 Chinese case-controlled studies
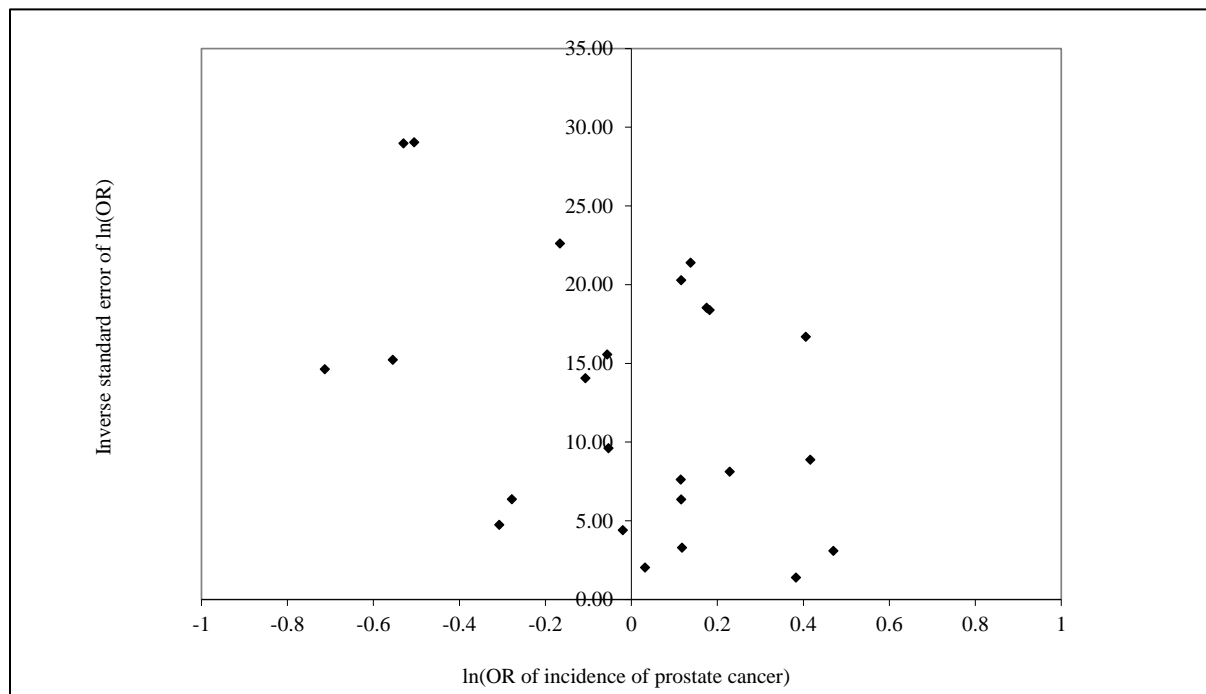
Table 3

Unadjusted mean odds ratio (OR) estimates of prostate cancer incidence and 95% confidence interval (CI) by studies with different controls, different definitions of drinkers for drinkers compared with 'abstainers' and controlled smoking status (N = 36) with tests of publication bias and heterogeneity

Subgroups	N †	Unadjusted mean OR		Egger's regression for publication bias		Test for heterogeneity	
		OR (95% CI)	T–test *p*	Coefficient	T–test *p*	Q statistic *p*	I^2 (%, 95% CI)
Non-drinker		1.00					
Control definition							
Hospital patients	27	1.41 (1.25 – 1.60)	0.0001	+1.09	0.2879	<0.001	60.36 (39.64 – 73.97)
Healthy control	9	1.43 (1.15 – 1.77)	0.0020	+0.54	0.6063	<0.001	44.67 (00.00 – 74.41)
T–test *p* ††			0.9377				
Drinker bias ‡							
No	14	1.29 (1.03 – 1.53)	0.0040	-1.11	0.2883	<0.001	44.51 (00.00 – 70.33)
Yes	22	1.50 (1.32 – 1.72)	0.0001	+1.82	0.0839	<0.001	61.61 (39.03 – 75.83)
T–test *p* ††			0.1566				
Drinker definition ‡‡							
Heavy or drank for 6+ months	19	1.52 (1.32 – 1.76)	0.0001	+2.10	0.0512	<0.001	58.70 (31.44 – 75.12)
Ever drank	17	1.31 (1.13 – 1.53)	0.0010	-0.13	0.8991	<0.001	49.05 (10.74 – 70.92)
T–test *p* ††			0.1604				
Controlled smoking ‡‡‡							
No	11	1.23 (1.02 – 1.48)	0.0313	-0.31	0.7611	<0.001	62.88 (28.79 – 80.65)
Yes	25	1.51 (1.33 – 1.71)	0.0001	+1.31	0.2041	<0.001	54.63 (28.73 – 71.12)
T–test *p* ††			0.0634				
Pooled all studies	36	1.42 (1.27 – 1.58)	0.0001	+1.07	0.2938	<0.001	56.87 (37.45 – 70.26)

† Number of OR estimates.

†† Test difference in RR between two subgroups.

‡ Studies that defined "Never drank/no drink" as reference were specified as no drinker bias; otherwise drinker bias.

‡‡ Heavy drink includes those studies that defined drinkers as those who drank at least one time for 6+ months, at least three times for 6+ months, at least three times for 10+ years, drink for 1+ year and 100+ g or 150+ g per day or drink >25 drinks per week.

‡‡‡ Smoking factor was controlled or not in study designs or analysis.

Table 4

Adjusted mean relative risk (RR) estimates of prostate cancer incidence by studies with different controls, reference group with and without former and occasional drinker bias and with different definitions of drinkers for drinkers compared with 'abstainers' (N = 36)

Subgroups	N †	Mean RR corrected for overestimated OR (A)		(A) Weighted and adjusted for between-study variation (B)		(B)Adjusted for types of control, control for smoking and types of drinker (C)	
		RR (95% CI)	T–test p	RR (95% CI)	T–test p	RR (95% CI)	T–test p
Non-drinker		1.00		1.00		1.00	
Control definition							
Hospital patients	27	1.41 (1.25 – 1.60)	0.0001	1.31 (1.12 – 1.565)	0.0040	1.32 (1.12 – 1.57)	0.0048
Healthy control	9	1.43 (1.15 – 1.77)	0.0020	1.62 (1.30 – 2.02)	0.0006	1.61 (1.25 – 2.06)	0.0020
T-test p ††			0.9377		0.0928		0.1495
Drinker bias ‡							
No	14	1.29 (1.09 – 1.53)	0.0040	1.42 (1.15 – 1.76)	0.0037	1.49 (1.15 – 1.92)	0.0071
Yes	22	1.50 (1.32 – 1.72)	0.0001	1.38 (1.17 – 1.62)	0.0011	1.43 (1.17 – 1.75)	0.0032
T-test p ††			0.1566		0.8080		0.8031
Drinker definition ‡‡							
Heavy or drank for 6+ months	19	1.52 (1.32 – 1.76)	0.0001	1.42 (1.20 – 1.68)	0.0009	1.50 (1.19 – 1.88)	0.0032
Ever drank	17	1.31 (1.13 – 1.53)	0.0010	1.36 (1.13 – 1.65)	0.0065	1.42 (1.16 – 1.74)	0.0036
T-test p ††			0.1604		0.7103		0.7036
Controlled smoking ‡‡‡							
No	11	1.23 (1.02 – 1.48)	0.0313	1.30 (1.07 – 1.59)	0.0125	1.45 (1.11 – 1.90)	0.0112
Yes	25	1.51 (1.33 – 1.71)	0.0001	1.46 (1.24 – 1.72)	0.0003	1.46 (1.21 – 1.76)	0.0013
T-test p ††			0.0694		0.3522		0.9779
Pooled all studies	36	1.42 (1.27 – 1.58)	0.0001	1.40 (1.24 – 1.58)	0.0001	1.46 (1.40 – 1.52)	0.0001

† N = Number of RR estimates (correct effect of OR overestimated RR in (A), further adjusted for sampling variability and between-study variation in (B) and further adjusted for types of control, drinker bias, defined drinkers and controlled smoking status in (C)).
†† test difference in RR between two subgroups.
‡ Studies that defined "Never drank/no drink" as reference were specified as no drinker bias; otherwise drinker bias.
‡‡ Heavy drink includes those studies that defined drinkers as those who drank at least one time for 6+ months, at least three times for 6+ months, at least three times for 10+ years, drink for 1+ year and 100+ g or 150+ g per day or drink >25 drinks per week.
‡‡‡ Smoking factor was controlled or not in study designs or analysis.

After correcting for the effect of OR overestimated RR (A – Table 4), we next estimated the weighted RR further adjusted for between-study variation (B) and the weighted RRs adjusted for between-study variation were further adjusted for potential confounding effects of types of controls, drinker bias, definitions of drinkers and controlled smoking status (C). These analyses are presented in Table 4. After correcting the effect of OR overestimated RR, the mean RR of 36 risk estimates did not change, i.e., RR being still 1.42 (95% CI: 1.27 – 1.58, P<0.0001) because the low incidence rate in Chinese population; the mean RR estimates also remained unchanged for all subgroups (Column A in Table 4). The weighted mean RR of 36 risk estimates was 1.40 (95% CI: 1.24 – 1.58, P<0.0001) after adjusting for the effect of between-study variation (Column B in Table 4). The fully adjusted RR was 1.46 (95% CI: 1.40 – 1.52,

P<0.0001) after further adjusting for the effects of types of controls, whether or not the studies controlled for smoking status, and how the studies defined reference group nondrinkers and drinkers in individual studies (Column C in Table 4). The fully-adjusted RRs for drinkers versus non-drinkers varied across subgroups but no significant differences were identified between subgroups.

Inclusion and/or exclusion for any study did not affect the mean risk estimate. After excluding of five articles or eight OR estimates published in English journals, the adjusted RR estimate remained unchanged. The sensitivity analyses of risk estimates are presented in Table 5.

Table 5

Sensitivity analysis of risk estimates of 25 case-control studies by exclusion one by one for analysis of the association of incidence risk of prostate cancer with alcohol consumption among Chinese people, 1994–2017

Author	Publication year	N of ORs	Unadjusted OR (95% CI) †	T–test *p*	Fully-adjusted RR (95% CI) ‡	T–test *p*
Hsing et al.	1994	3	1.47 (1.33 – 1.63)	0.0001	1.40 (1.36 – 1.45)	0.0001
Wei et al.	1994	1	1.43 (1.28 – 1.60)	0.0001	1.45 (1.40 – 1.51)	0.0001
Lee et al.	1998	1	1.41 (1.26 – 1.58)	0.0001	1.48 (1.40 – 1.57)	0.0001
Zhang et al.	1999	1	1.40 (1.26 – 1.57)	0.0001	1.40 (1.34 – 1.47)	0.0001
Jian et al.	2004	2	1.43 (1.27 – 1.60)	0.0001	1.46 (1.39 – 1.52)	0.0001
Yang et al.	2006	1	1.43 (1.27 – 1.59)	0.0001	1.48 (1.41 – 1.56)	0.0001
Liang et al.	2007	4	1.39 (1.23 – 1.56)	0.0001	1.43 (1.38 – 1.49)	0.0001
Xu et al.	2007	1	1.41 (1.26 – 1.58)	0.0001	1.44 (1.38 – 1.51)	0.0001
Li et al.	2008	1	1.43 (1.28 – 1.60)	0.0001	1.51 (1.42 – 1.61)	0.0001
Wu et al.	2008	4	1.41 (1.24 – 1.59)	0.0001	1.44 (1.37 – 1.50)	0.0001
Wu et al.	2010	1	1.44 (1.29 – 1.60)	0.0001	1.46 (1.42 – 1.51)	0.0001
Xu et al.	2010	1	1.40 (1.26 – 1.57)	0.0001	1.47 (1.38 – 1.56)	0.0001
Lu et al.	2011	1	1.44 (1.29 – 1.60)	0.0001	1.50 (1.42 – 1.58)	0.0001
Wu et al.	2011	1	1.41 (1.26 – 1.58)	0.0001	1.45 (1.39 – 1.52)	0.0001
Zhang et al.	2011	1	1.41 (1.26 – 1.58)	0.0001	1.47 (1.39 – 1.55)	0.0001
Min et al.	2012	1	1.40 (1.26 – 1.57)	0.0001	1.42 (1.37 – 1.47)	0.0001
Shao et al.	2012	1	1.41 (1.26 – 1.57)	0.0001	1.44 (1.38 – 1.50)	0.0001
Zhang et al.	2012	1	1.39 (1.25 – 1.55)	0.0001	1.48 (1.38 – 1.59)	0.0001
Jia et al.	2013	2	1.41 (1.26 – 1.58)	0.0001	1.50 (1.39 – 1.52)	0.0001
Liu et al.	2014	2	1.41 (1.26 – 1.58)	0.0001	1.44 (1.37 – 1.52)	0.0001
Liu et al.	2014	1	1.41 (1.26 – 1.58)	0.0001	1.45 (1.38 – 1.53)	0.0001
Ma et al.	2014	1	1.44 (1.29 – 1.60)	0.0001	1.48 (1.41 – 1.55)	0.0001
Wang et al.	2014	1	1.42 (1.27 – 1.59)	0.0001	1.51 (1.41 – 1.52)	0.0001
Dong et al.	2016	1	1.42 (1.27 – 1.59)	0.0001	1.48 (1.40 – 1.57)	0.0001
Wei et al.	2017	1	1.40 (1.25 – 1.56)	0.0001	1.41 (1.34 – 1.48)	0.0001
Cancer control ††	1994	2	1.46 (1.32 – 1.62)	0.0001	1.41 (1.37 – 1.46)	0.0001
Articles/Mandarin	1994-2008	8	1.52 (1.35 – 1.71)	0.0001	1.48 (1.41 – 1.55)	0.0001
36 risks pooled	**1994-2017**	**36**	**1.42 (1.27 – 1.58)**	**0.0001**	**1.46 (1.40 – 1.52)**	**0.0001**

† Unadjusted OR by excluding each study.
‡ Fully-adjusted RR by excluding each study.
†† Two risk estimates used other cancer patients as controls Hsing et al. (1994) and Wei et al. (1994).

We conducted sensitivity analyses by including or excluding each of the studies in meta-regression in order to examine their effects.

The dose-response analysis showed that drinkers who drank 1-55 g per day, 56-100 or over 100 had a significantly higher risk of suffering from prostate cancer than healthy/patient controls (OR=1.51, 1.43 or 1.59). The OR significantly increased as drinking alcohol amount increased per day (Wald test P<0.001).

Table 6

Estimated odds ratio (OR) and 95% confidence interval (CI) of prostate cancer for three drinking groups versus non-drinkers among Chinese people

Ethanol grams per day	Number of cases and controls †				Healthy people as control				Patient as control				Healthy/patient as control			
	Cases	HC	DC	HP	OR	95%	CI	x^2P	OR	95%	CI	x^2P	OR	95%	CI	x^2P
Jian et al. 2004																
Non-drinker	60	142			1.00											
1-55 g	38	70			1.28	0.78	2.11	ns								
56+ g	32	62			1.22	0.72	2.06	ns								
Liang et al. 2007																
Non-drinker	96	106	109	215	1.00				1.00				1.00			
1-100	25	21	17	38	1.31	0.69	2.50	ns	1.67	0.85	3.28	ns	1.47	0.84	2.58	ns
101+	21	15	16	31	1.55	0.75	3.17	ns	1.49	0.74	3.02	ns	1.03	0.49	2.18	ns
Wu et al. 2008																
Non-drinker	44	47	51	98	1.00				1.00				1.00			
1-100	6	5	5	10	1.28	0.37	4.50	ns	1.39	0.40	4.87	ns	1.34	0.46	3.91	ns
101+	12	10	6	16	1.28	0.50	3.26	ns	2.32	0.80	6.69	ns	1.25	0.35	4.40	ns
Liang et al. 2007+Wu et al. 2008																
Non-drinker	140	153	160	313	1.00				1.00				1.00			
1-100	31	26	22	48	1.30	0.74	2.30	ns	1.61	0.89	2.91	ns	1.44	0.88	2.37	ns
101+	33	25	22	47	1.44	0.82	2.55	ns	1.71	0.95	3.08	ns	1.09	0.58	2.05	ns
All 25 included studies																
Non-drinker	3,087	2,450	3,671	6,122	**1.00**				**1.00**				**1.00**			
1-55 g	371	221	268	489	**1.33**	1.12	1.59	**	**1.65**	1.40	1.94	***	**1.51**	1.31	1.74	***
56-100 g	312	196	237	433	**1.26**	1.05	1.53	*	**1.57**	1.32	1.87	***	**1.43**	1.23	1.67	***
101+	728	400	505	905	**1.44**	1.26	1.65	***	**1.71**	1.52	1.94	***	**1.59**	1.43	1.77	***
Drinker	1,411	817	1,010	1,826	**1.37**	1.24	1.52	***	**1.66**	1.51	1.83	***	**1.53**	1.41	1.66	***

† HC=healthy people as control, DC=disease people as controls and HP=combined healthy and patient controls. Wald test: ns P>0.05 *P<0.05 **P<0.01 ***P<0.001.

Discussion

We present a meta-regression analysis of the case-control studies examining the relationship between incidence of prostate cancer and alcohol consumption in Chinese population. The study included 25 studies with 36 OR estimates to produce mean RR of prostate cancer due to alcohol use.

The analysis shows a 46% significantly increased RR of prostate cancer for drinkers versus non-drinkers (RR: 1.46, 95% CI: 1.40 – 1.52) after adjusting for the effects of overestimated RR using ORs in case-control studies, sampling variability and between-study variation and the effects of using different controls, controlled smoking status and differently defining drinkers/non-drinkers in the individual studies. The dose-response analysis showed that the risk of prostate cancer significantly increased as drinking alcohol amount increased per day. These risk estimates are consistent with that estimated in other published meta-analysis (Zhao et al., 2016) but markedly higher in this study than that one (RR=1.46 vs 1.08).

Among 36 RR estimates in 25 studies, 9 used "healthy people" as controls and 27 used patients as controls. The RR estimate using healthy people as controls had a markedly higher RR than that using patients as controls (1.61 vs 1.32). This was because alcohol consumption caused many diseases (Rehm, Gmel, Sempos, & Trevisan, 2003) and thus using patients as controls could underestimate the RR of prostate cancer. Further research should avoid using patients as controls.

Sixteen of the 25 included studies have clearly misclassified former drinkers and occasional or light drinkers into the lifetime non-drinkers. The other nine studies specified non-drinker reference groups as "never drank or no drink". Studies have shown that including former and occasional drinkers in the non-drinking reference or comparisons group tends to underestimate the risk of prostate cancer for drinkers (Shaper, Wannamethee, & Walker, 1988; Stockwell et al., 2016). The meta-analysis on prostate cancer and alcohol use by Zhao et al. (2016) showed an 8% increase in the RR of prostate cancer of any drinking versus non-drinking in the studies without former and occasional drinker biases compared with that in the studies with both former and occasional drinker biases. Our analysis showed a 6% difference in fully adjusted RR estimates among Chinese population.

The adjusted mean of 19 RR estimates in 15 studies that defined drinkers as those who drank at least one time for 6+ months, at least three times for 6+ months, at least three times for 10+ years, drink for 1+ year and 100+ g or 150+ g per day or drink >25 drinks per week was higher than that of other 17 RR estimates. This suggested that heavy drinkers had a higher risk of prostate cancer incidence.

Alcohol is a known carcinogen causing a variety of human cancers (World Cancer Research Fund/American Institute for Cancer Research, 2007) via different biological pathways depending on the anatomical site. The evidence that alcoholic drinks are a cause of cancers of the mouth, pharynx, larynx, oesophagus, liver, colorectum and breast in women is compelling (Bagnardi et al., 2001; English, Holman, D'Arcy, & Australia Department of Community Services and Health National Drug Strategy, 1995; World Cancer Research Fund/American Institute for Cancer Research, 2007). Alcoholic beverages are multicomponent mixtures containing several carcinogenic compounds such as ethanol, acetaldehyde, aflatoxins and ethyl carbamate (Lachenmeier, Przybylski, & Rehm, 2012) and all of these compounds may contribute to increase the risk of cancer due to alcohol consumption reported in observational studies. The biological mechanisms by which alcohol intake might increase the risk of prostate cancer are not fully understood but the main mechanisms are likely to include a genotoxic effect of acetaldehyde, the induction of microsomal cytochrome P450 2E1 (CYP2E1) and associated oxidative stress, increased estrogen concentration, a role as a solvent for tobacco carcinogens, changes in folate metabolism, and changes in DNA repair (Baan et al., 2007; Homann et al., 2006; International Agency for Research on Cancer [IARC] 2010).

There are several limitations with this meta-analysis. Our meta-analysis was based on 25 studies including 36 risk estimates. This sample is relatively small when conducting multivariate meta-regression to control for study level characteristics that might confound the relationship between prostate cancer and alcohol consumption. While there were relatively few studies available for this analysis, the required number of observations per variable for linear regression is much smaller than in logistic regression. According to Austin and Steyerberg (2015) even two subjects per variable would not bias an estimate made using linear regression analysis (Austin & Steyerberg, 2015). Furthermore, adjustment for study level characteristics such as whether smoking status was controlled is of course not as precise as controlling for this variable at the individual level within a study. Uncontrolled confounding from unmeasured or imprecisely measured variables will be present both within and between studies. The great majority of identified studies suffered one or more serious methodological problems including the widespread practice of misclassifying former drinkers as abstainers. This study identified only 25 case-control studies which 22 of these studies investigated the risk of prostate cancer among Chinese drinkers versus non-drinkers defined by the authors and the dose-response relationship cannot be examined using all 25 included studies. There were three studies that classified subjects into three levels of drinking. The cases and controls can be distributed into categories of non-drinkers, drinkers who drank 1-55 g, 56-100 g and more than 100 g per day according to the distributions of cases and controls in these three studies. We assumed that cases and controls had the same distributions of non-drinkers and drinkers in each of 25 studies and thus estimated the number of non-drinkers and drinker in three drinking groups. The analysis found that the OR significantly increased as drinking alcohol amount increased per day.

The measures of alcohol consumption in these studies are mostly imprecise, including nine studies that specified "never drank" or "no drinking" as the reference group and thus may largely have confounded the risk estimates. However, it was expected that all the studies underestimated risk estimates using the definitions of drinkers versus non-drinkers and the present risk estimates can be considered conservative. This study was unable to incorporate the recommendation from Liang and Chikritzhs (2013) that former drinkers should in fact be included within the category of current drinkers according to previous drinking level so as to create an unbiased estimate of the risk relationship. For example, Hayes and colleagues (1996) found that among both blacks and whites, the risk associated with alcohol use was similarly increased among both recent (current drinker or quit in the last year) and former consumers of alcohol.

In summary, there is a significantly higher risk of prostate cancer incidence among Chinese drinkers than non-drinkers. The estimated risk is markedly higher in Chinese population than in the Caucasian population. Few Chinese studies examined the dose-response relationship and no cohort studies were identified in Chinese databases and in previously published reviews and meta-analyses. Future case-control and cohort studies should consider these issues which may have affected the estimated risk of prostate cancer due to alcohol consumption and investigate the dose-response relationship in the Chinese population. We recommend that future studies on alcohol and disease seek to avoid biasing risk estimates by misclassifying either (i) former or occasional drinkers as abstainers, or (ii) occasional drinkers as low volume drinkers. We also recommend that former drinkers are classified with drinkers according to their past level of consumption.

Declarations

Ethics approval and consent to participate: Research ethics committee review and approval were not required, as aggregate data were extracted from published studies. Authors of some studies were contacted to clarify relevant information in the studies but no information on individuals in the studies was requested.

Role of the funding sources: The study funders had no role in study design, data collection, analysis or interpretation, report preparation and the decision to publish. All authors had full access to all the data and had final responsibility for the decision to submit for publication.

Consent for publication: Not applicable.

Availability of data and material: All data generated and analyzed during this study are included in this published article and can be found in Appendix A: Meta-analysis data on prostate cancer and alcohol consumption in Chinese population.

Competing Interests: None.

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