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ORIGINAL ARTICLE

Prostate Disease

Effect of statins type on incident prostate cancer risk: a meta-analysis and systematic review

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The aim of this study is to investigate the effect of statins type or even when grouping statins by hydrophilic or hydrophobic nature on prostate cancer risk. A literature search was performed without language restrictions using the databases of PubMed (1984.1–2015.3), MEDLINE (1984.1–2015.3), and EMBASE (1990.1–2015.3). Two independent reviewers appraised eligible studies and extracted data. Weighted averages were reported as relative risk (RR) with 95% confidence intervals (CI). Statistic heterogeneity scores were assessed with the standard Cochran's *Q*-test and I^2 statistic. Publication bias was detected using the Begg's and Egger's tests. All statistical analyses were conducted by STATA version 10. Finally, fourteen studies were included in the meta-analysis. Both hydrophilic and hydrophobic statins showed no association with incidence of prostate cancer (RR = 1.00, 95% CI: 0.82–1.17; RR = 0.90, 95% CI: 0.73–1.08, respectively). Meanwhile, the risk of prostate cancer was not reduced in simvastatin (RR = 0.89, 95% CI: 0.72–1.05), pravastatin (RR = 1.02, 95% CI: 0.94–1.11), atorvastatin (RR = 0.89, 95% CI: 0.76–1.02), fluvastatin (RR = 0.99, 95% CI: 0.97–1.01), or lovastatin users (RR = 0.94, 95% CI: 0.79–1.08). The funnel plot showed that there was no publication bias. The results showed that statins had a neutral effect on prostate cancer risk; hydrophilic and hydrophobic statins as well as any subtype of statins did not affect the risk of prostate cancer.

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INTRODUCTION

Statins, also known as 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase) inhibitor, are widely used to lower the cholesterol levels. Prostate cancer (PCa) is the most common solid tumor in men from western countries and the second leading cause of death,[1,2] while in China, it is the sixth common solid cancer and the tenth leading cause of death.[3] Recently, a climbing amount of evidence on the anticancer effects of statins has become available. Although some studies found that statins had a neutral effect on PCa and PCa death risk,[4,5] the other studies showed that statins lowered the risk of prostate cancer.[6] In addition, some trials showed that the long-latency positive effects remained possible[4] while some studies found a neutral effect of long-term statins use on PCa risk.[6,7] All relevant meta-analyses found that statins could lower the risk of advanced prostate cancer.[4–8] However, whether statins type also contributed to the inconformity of results and affected the statins' effect on PCa risk remained unknown.[9–13] Thus, it is necessary to conduct a systematic review and meta-analysis to comprehensively evaluate the association between commonly used types of statins and PCa risk.

METHODS

Study selection

We performed a literature search without language restrictions using the databases of PubMed (1984.1–2015.3), MEDLINE (1984.1–2015.3), EMBASE (1990.1–2015.3), the Cochrane Library, Web of Science, and ClinicalTrials.gov to identify clinical trials of statins use with a primary or secondary endpoint of PCa diagnosis or PCa death. A search strategy using the Medical Subject Heading and text keywords "statins", "HMG-CoA reductase inhibitor", "atorvastatin", "cerivastatin", "fluvastatin", "lovastatin", "mevastatin", "pravastatin", "rivastatin", "rosuvastatin", "simvastatin", "cancer(s)," "carcinoma(s)", "neoplasm(s)", "tumour(s)", and "malignancy(ies)" was used. The search strategy was adjusted to adapt different databases. A manual search of abstracts published after 1990 at the American Heart Association, the American College of Cardiology, the American Society of Clinical Oncologists, the American Urological Association, and the American Society of Hematology was conducted. In addition, we conducted a manual search in published articles to identify the additional relevant studies. After removing duplicate publications, two reviewers (Ping Tan and Shi-You Wei) independently assessed all the remaining results by checking titles and abstracts. Studies investigating the association between statins and PCa were considered for further full-text assessment. We adapted a PRISMA flowchart to depict the study selection.

Inclusion and exclusion criteria

Included studies focused on men of all ages without PCa before using statins. The inclusion criteria including (1) clearly defined exposure

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to statins; (2) statins' types were available; (3) incidence of PCa as the one interested outcome; (4) hazard ratio (HR), relative risk (RR), or odds ratio (OR) with 95% confidence intervals (CIs) or primary data for their calculation were available. All randomized controlled trials (RCTs), cohort studies, and case–control studies with both full-text articles and abstracts associated with the topic were considered to be eligible. Letters to the editor, comments, editorials, case reports, and animal studies were excluded. When studies reported outcomes from similar or overlapping databases or cohorts, only data from the most recent publication were included. Studies that were not published in the English language were also excluded. The primary outcome is to evaluate the effect of different statins types on PCa risk.

Quality assessment

Two reviewers (Ping Tan and Shi-You Wei) independently used the Newcastle–Ottawa Scale (NOS) to assess the quality of the observational studies included (cohort and case–control studies).[14] NOS comprises three parts (selection, comparability, and exposure for case–control studies or outcome for cohort studies) and scores of 4, 2, and 3 are assigned for these three parts, respectively. Studies with scores of 0–3, 4–6, and 7–9 were considered as low, moderate, and high quality, respectively. The quality assessment of RCTs was conducted using the modified Jadad scale,[15] which gave the following scores: generation of the allocation sequence (2), concealment of allocation (2), blinding (2), and incomplete outcome data (1). Scores of 1–3 indicate low quality and 4–7 indicate high quality.

Data extraction and analysis

Data from each study were independently extracted by the two reviewers. Hydrophilic statins included pravastatin, rosuvastatin, atorvastatin, and fluvastatin; hydrophobic statins included lovastatin and simvastatin. RR effect estimates with their 95% CIs were used to assess potential association between statins type and PCa risk, as HR and OR were broadly equivalent to RR when disease incidence was low.[16,17] Statistic heterogeneity scores were assessed with the standard Cochran's *Q*-test with a significance level of $\alpha = 0.10$. I^2 statistic was also used to quantify inconsistency across studies to assess the impact of meta-analysis heterogeneity. I^2 >50% indicates a considerable level of heterogeneity. When a significant heterogeneity was observed, random-effect model was used, otherwise the fixed-effect model was accepted. Publication bias was detected using the Begg's and Egger's tests. Statistical significance was determined using the two-tailed test where $P < 0.05$ was considered statistically significant. All statistical analyses were conducted by STATA version 10 (Stata Corporation, College Station, TX, USA).

RESULTS

Our initial search yielded 8633 citations. After employing exclusion criteria, 19 studies were remained in the meta-analysis (**Figure 1**).[9–13,18–31] PCa patients were confirmed by positive prostate biopsy during the follow-up. A total of 104 707 PCa patients were included in the analysis as well as more than 1.6 million subjects. **Table 1** and **2** show the characteristics of the studies included. Three studies revealed an inverse association between hydrophobic statins and PCa risk[10,11,13] while only one found a lowered risk of PCa among hydrophilic users.[12] Different effect on incident PCa risk between hydrophilic and hydrophobic statins was observed in five trials.[9–13] The effect of simvastatin, lovastatin, atorvastatin, fluvastatin, and pravastatin on PCa risk was available for meta-analysis. The definitions of statins users and duration of statins use were various among studies (**Table 1** and **2**).

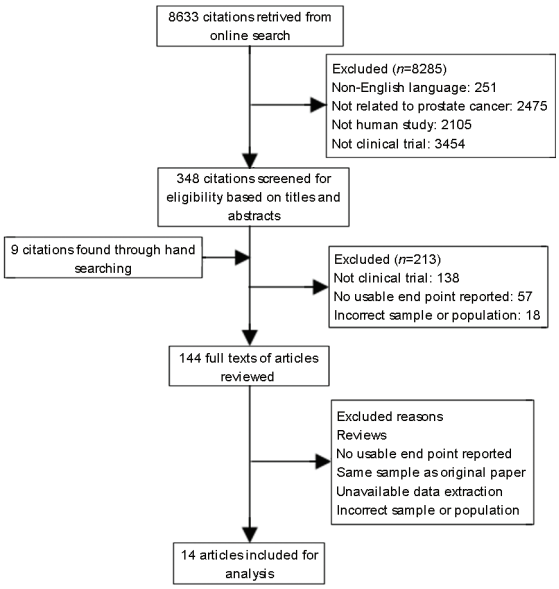

Figure 1: Trial identification, inclusion, and exclusion.

In this meta-analysis, we found that there was no obvious evidence supporting that hydrophilic or hydrophobic statins could reduce the incidence risk of PCa (RR = 1.00, 95% CI: 0.82–1.17; RR = 0.90, 95% CI: 0.73–1.08, respectively) (**Figure 2** and **3**). High heterogeneities existed among studies evaluating hydrophilic and hydrophobic statins ($I^2 = 68.8\%$, $P = 0.001$, and $I^2 = 94.9\%$, $P < 0.001$, respectively). Then, subgroup analyses were performed on the basis of the study design. The pooled results of four cohort studies and three RCTs both showed that hydrophobic statins had a neutral effect on PCa risk. However, a positive impact on PCa risk was observed in the result of three case–control studies (HR = 0.95, 95% CI: 0.92–0.99). In terms of hydrophilic statins, results of both cohort studies and case–control studies as well as RCTs showed a neutral effect on PCa incidence. However, high heterogeneities still existed among cohort studies. The details are shown in **Table 3**.

Five commonly used statins' brands were evaluated in subgroups; however, no statistically significant effect was seen in simvastatin (RR = 0.89, 95% CI: 0.72–1.05) (**Figure 4**), pravastatin (RR = 1.02, 95% CI: 0.94–1.11) (**Figure 5**), atorvastatin (RR = 0.89, 95% CI: 0.76–1.02), fluvastatin (RR = 0.99, 95% CI: 0.97–1.01), or lovastatin users (RR = 0.94, 95% CI: 0.79–1.08) (**Table 3**). As results shown in **Table 3**, simvastatin and atorvastatin as well as fluvastatin had a neutral effect on PCa incidence risk in all subgroups. A benefit impact of lovastatin on PCa risk was observed in result of two cohort studies while a neutral effect was found in pooled outcome of two case–control studies. In terms of pravastatin, it did not affect PCa risk in pooled result of three cohort studies or the two RCTs while a negative effect of pravastatin was observed in the result of two case–control studies.

Studies of low quality, such as Coogan *et al.*[18] and HPSC Group,[24] have been further excluded in subgroup analyses to confirm their effect on results. However, the results remained stable and presented the same trend as before (data was not shown).

Funnel plot showed that there were no publication bias among studies exploring the effect of hydrophilic or hydrophobic statins on PCa risk (Begg's $P = 1.0$, Egger's $P = 0.98$; and Begg's $P = 0.59$, Egger's $P = 0.53$, respectively; **Figure 6**). Sensitivity analysis results remained stable and no significant variability was found (data not shown).

Table 1: Characteristics of cohort studies and RCTs included in the meta-analysis

Sources	*Country*	*PCa cases (n)/ statin group (n)*	*PCa cases (n)/ control group (n)*	*Statin type*	*Mean follow-up time (year)*	*Duration of follow-up (year)*	*Quality score*
Nordström *et al.*[9]	Sweden	2321/4825	5233/11 923	a, b	NR	6 (2007–2012)	8
Lustman *et al.*[10]	Israel	399/37 645	990/29 096	a, b, c, d, e, f, g, h	NR	9 (2001.1–2009.12)	8
Fowke *et al.*[26]	USA	319/783	525/1365	c, d	NR	8 (2002–2010)	7
Haukka *et al.*[27]	Finland	562/5871	489/5057	c, d, e, f, g	3.06	10 (1996.1–2005.12)	8
Hippisley-Cox and Coupland[28]	England	7129/990 495*		c, d, e, g, h	NR	6 (2002.1–2008.6)	7
Murtola *et al.*[12]	Finland	268/6692	1326/16 516	a, b, c, d, e	6.92	9 (1996–2004)	8
Boudreau *et al.*[13]	USA	246/12 013	2286/71 359	a, b	3.3	18 (1990–2007)	7
Ford *et al.*[25,#]	Scotland	89/3291	59/3286	g	13.2	15 (1989.2–2004.12)	7
HPSC group[24,#]	UK	145/7727	145/7727	c	5	NR	3
Strandberg *et al.*[23,#]	Multicenter	51/1814	55/1803	c	10	NR	7
The LIPID study group[21,#]	Multicenter	148/3756	145/3742	g	8.0	2 (1990–1992)	4
Serruys *et al.*[22,#]	Multicenter	2/844	2/833	e	3.9	5 (1996–2001)	5
Downs *et al.*[20,#]	USA	109/2805	108/2803	f	5.2	7 (1990–1997)	5

*A total of 7129 patients diagnosed with PCa in 990 495 males during the study period. #Randomized controlled trial. a: hydrophilic; b: hydrophobic; c: simvastatin; d: atorvastatin; e: fluvastatin; f: lovastatin; g: pravastatin; h: rosuvastatin; RCT: randomized controlled trial; PCa: prostate cancer; NR: not reported

Table 2: Characteristics of case–control studies included in the meta-analysis

Sources	*Country*	*Participants (n)*	*Statin users (n)*	*Statin users (n)/ cases (n)**	*Statin users (n)/ controls (n)*	*Statin type*	*Mean follow-up time (month)*	*Duration of follow-up (year)*	*Quality score*
Jespersen *et al.*[11]	Denmark	254 880	47 299	7125/41 690	35 485/208 501	a, b	NR	13 (1997–2010)	7
Vinogradova *et al.*[29]	UK	76 617	14 282	2774/14 764	11 508/61 853	c, d, g	28	10 (1998.1–2008.7)	7
Coogan *et al.*[18]	USA	3374	526	250/1367	178/2007	a, b	NR	16 (1992–2008)	3
Agalliu *et al.*[19]	USA	1943	554	272/1001	244/942	a, b	NR	4 (2002.1–2005.12)	5
Murtola *et al.*[30]	Finland	49 446	5061	2622/24 723	2439/24 723	c, d, e, f, g	NR	7 (1995–2002)	6
Shannon *et al.*[31]	USA	302	133	34/100	99/202	c, f	NR	7 (1997–2004)	4

*Prostate cancer cases. a: hydrophilic; b: hydrophobic; c: simvastatin; d: atorvastatin; e: fluvastatin; f: lovastatin; g: pravastatin; NR: not reported

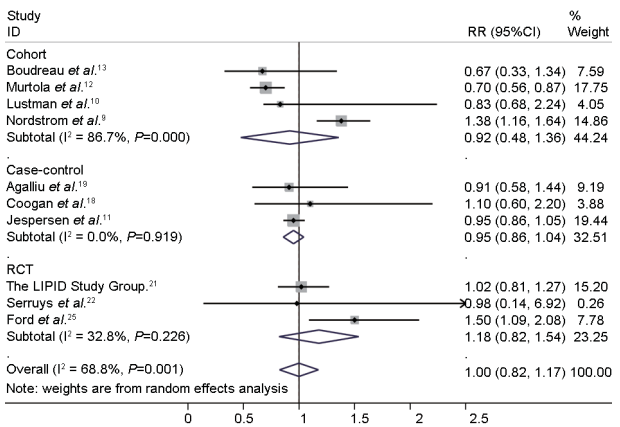

Figure 2: The effect of hydrophilic statins on incident prostate cancer risk. RR: relative risk; CI: confidence interval; RCT: randomized controlled trial.

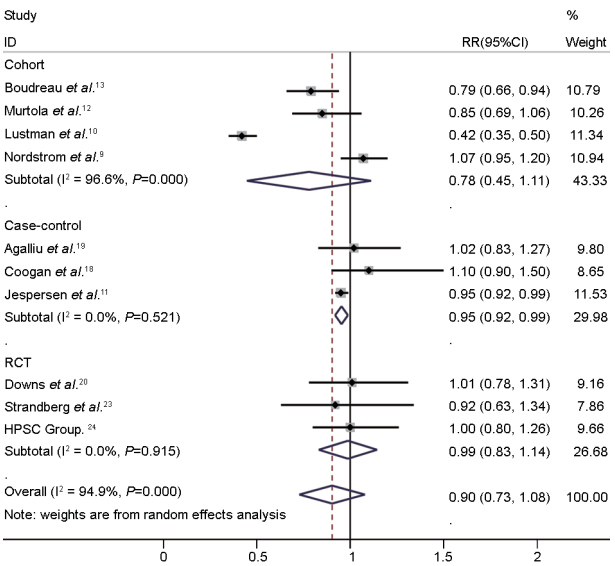

Figure 3: The effect of hydrophobic statins on incident prostate cancer risk. RR: relative risk; CI: confidence interval; RCT: randomized controlled trial.

DISCUSSION

To our knowledge, this is the first meta-analysis analyzing the effect of statins' types and brands on PCa incidence. In the past decade, the role of statins in the development of PCa has been increasingly discussed; however, their effect is controversial.[4–7,32] In this meta-analysis, hydrophilic and hydrophobic statins as well as any subtype of statin did not affect the risk of PCa. Although a small benefit of lovastatin to PCa was found in synthesis of two cohort studies, this effect was untrusted because of few studies and the reverse result in case–control studies. Similarly, pravastatin's adverse effect on PCa risk could not be confirmed either.

High heterogeneities were observed in the overall analyses. Then, subgroup analyses were conducted on the basis of the study design. The heterogeneities were lowered in some subgroups, which suggested that the study design and statins type might contribute to them. In addition, duration of statins use and various definition of statin users might also affect the heterogeneities.

Table 3: The pooled estimates of meta-analysis in subgroups

Outcomes	*Studies (n)*	*Pooled estimates*		*I^2 statistic (P)*
		RR	*95% CI*	
Hydrophobic				
Total	10	0.90	0.73–1.08	<0.001
Cohort studies	4	0.78	0.45–1.11	<0.001
Case–control studies	3	0.95	0.92–0.99	0.521
RCT	3	0.99	0.83–1.14	0.915
Hydrophilic				
Total	10	1.00	0.82–1.17	0.001
Cohort studies	4	0.92	0.48–1.36	<0.001
Case–control studies	3	0.95	0.86–1.04	0.919
RCT	3	1.18	0.82–1.54	0.226
Atorvastatin				
Total	7	0.89	0.76–1.02	<0.001
Cohort studies	5	0.82	0.60–1.04	<0.001
Case–control studies	2	1.03	0.93–1.13	0.181
Fluvastatin				
Total	6	0.99	0.97–1.01	0.953
Cohort studies	4	0.99	0.97–1.01	0.775
Lovastatin				
Total	5	0.94	0.79–1.08	0.008
Cohort studies	2	0.94	0.93–0.96	0.362
Case–control studies	2	0.73	0.05–1.42	0.001
Pravastatin				
Total	7	1.02	0.94–1.11	0.086
Cohort studies	3	0.96	0.87–1.05	0.220
Case–control studies	2	1.14	1.01–1.26	0.774
RCT	2	1.19	0.77–1.60	0.108
Simvastatin				
Total	10	0.89	0.72–1.05	<0.001
Cohort studies	5	0.86	0.58–1.14	<0.001
Case–control studies	3	0.96	0.80–1.11	0.005
RCT	2	0.98	0.78–1.17	0.711

RR: relative risk; CI: confidence interval; RCT: randomized controlled trial

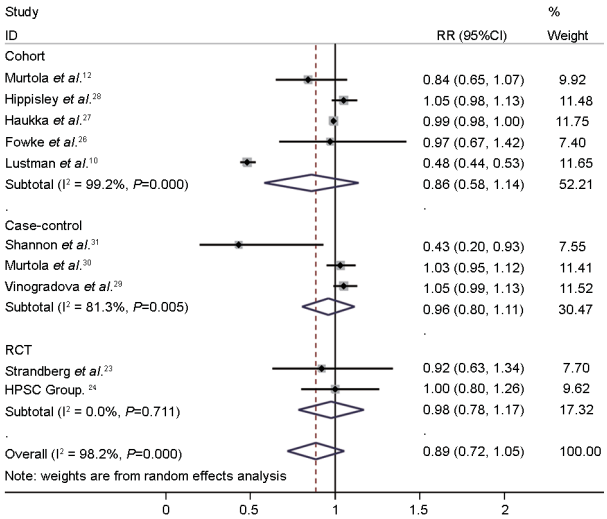

Figure 4: The effect of simvastatin on incident prostate cancer risk. RR: relative risk; CI: confidence interval; RCT: randomized controlled trial.

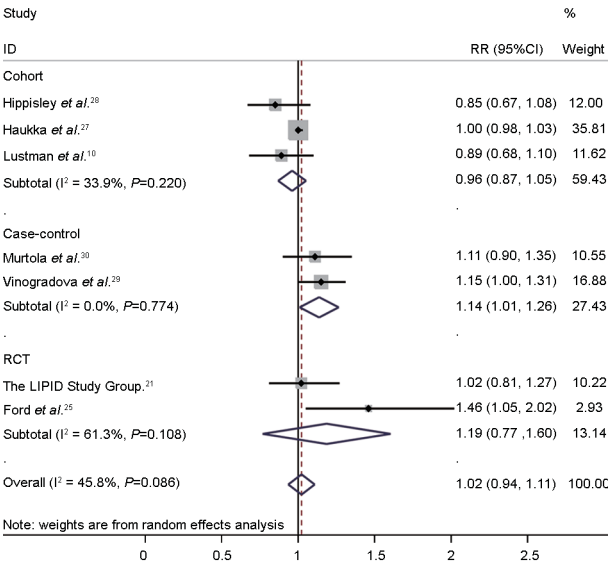

Figure 5: The effect of pravastatin on incident prostate cancer risk. RR: relative risk; CI: confidence interval; RCT: randomized controlled trial.

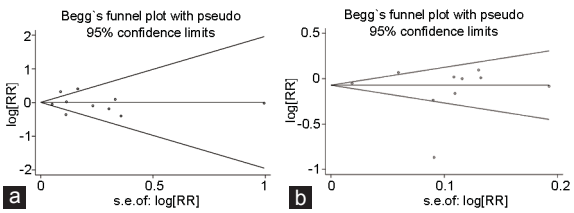

Figure 6: Funnel plot for publication bias of studies evaluating hydrophilic (**a**) and hydrophobic (**b**) statins' effect on incident prostate cancer risk. RR: relative risk; s.e.: standard error.

Previous researches demonstrated that statins had ability to kill PCa cells through inhibiting HMG-CoA reductase, causing a pronounced reduction in serum cholesterol and may lead to a decreased formation of lipid rafts and promote cancer cell apoptosis.[33] Meanwhile, statins, via inhibiting lipid raft signaling, inflammation, inducing cell cycle arrest and apoptosis, and anti-angiogenesis, performed an effect on prostate tumorigenesis.[34–36] Moreover, simvastatin, lovastatin, and fluvastatin had shown to inhibit PCa cell proliferation,[37] through downregulating the insulin-like growth factor 1 receptor.[38] One previous study has suggested that lipophilic statins have greater lipid solubility and more readily permeate cell membranes to exert potential anticancer effects,[39–41] but this was not evident in our study. Meanwhile, as lipophilic agents were limited in available trials, the pooled estimates of previous meta-analyses may have been diluted. In addition, another trial thought that hydrophilic statins, with their impaired ability to penetrate biological membranes, might perform better than lipophilic statins which readily entered cells. But this difference was not observed in our study.[42]

Statins use could lower the risk of PCa compared with nonusers in some previous studies.[6,10,11,43,44] However, some other studies found that there was no association between statins and PCa risk.[4,5,7,20,45–49] Previous studies reported that this inconsistence might be attributed to prostate-specific antigen (PSA) testing, causing the detection bias, and statins dosage.[12,30] Comparing with duration of statins use, statins dosage or cumulative amount of statins use might perform a stronger relation to PCa risk, as the drug usage was irregular with months of nonuse between periods of use.[6,12] In addition, statins dosage of *in vitro* studies reporting growth inhibition in prostate-derived cell lines, was much higher than standard therapeutic use. Our results showed that

no subtype of statin affected the risk of Pca; thus, we could believe that subtype of statin did not affect the statins' effect on the incidence of PCa risk.

Our meta-analysis had some limitations. First, this study was limited by the small number of studies and patients that were available for analysis. Second, the study design, definition of drug exposure, and usage of statins type among included studies were diverse, which might contribute to significant heterogeneities observed in subgroups. To minimize the confounding biases in this meta-analysis, we chose multivariable adjusted-effect estimates to pool the effects, and subgroup analyses were conducted on the basis of the study design. Furthermore, the effect of various statins type on advanced PCa was not available at the moment, thus whether statins type affected the risk of advanced PCa remained to be seen. In addition, duration of follow-up was limited in all included studies; only 2 trials were followed up over 5 years and most studies did not report mean follow-up time. Thus, whether long-term statins use could affect PCa risk was unavailable for meta-analysis. Finally, only one randomized controlled trials reporting the effect of pravastatin on PCa risk was available at present,[25] lowering the precision of our results. Thus, more future studies should be randomized designed.

CONCLUSIONS

We conclude that statins had a neutral effect on the incident PCa risk, both hydrophilic and hydrophobic, and no subtype of statins affect the risk of PCa (simvastatin, atorvastatin, fluvastatin, pravastatin, and lovastatin). As most studies had relatively short follow-up, it will be important for future studies to explore long-latency effects of statins on PCa and to rule out their effects on incident advanced PCa risk.

AUTHOR CONTRIBUTIONS

QW, LY, and PT conceived this review. PT, CZ, and SYW identified reports of trials and extracted data. LG provided statistical advice and CZ did all statistical analyses. ZT checked for statistical inconsistency and interpreted data. LY, PT, and CZ contributed to data interpretation. PT drafted the report and all other authors (QW, LY, CZ, SYW, ZT, and LG) critically reviewed the article. All authors read and approved the final manuscript.

COMPETING INTERESTS

The authors declared no competing interests.

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