Int J Clin Exp Med 2018;11(9):8873-8885
www.ijcem.com /ISSN:1940-5901/IJCEM0073724

Review Article

The association of statin use with risk of kidney, bladder and prostate cancer: a systematic review and meta-analysis of cohort studies

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Received Augustl 3, 2017; Accepted June 4, 2018; Epub September 15, 2018; Published September 30, 2018

Abstract: Background: Emerging evidence suggested that statins might decrease the risk of cancer. This study examined the associations of statin use with the risk of main urologic cancer, and a sex-specific relationship between statin use and the risk of cancer was also evaluated. Methods: A literature search in PubMed, MEDLINE, and Web of Science databases was undertaken through February 2017 evaluating the association between statin use and risk of main urologic cancer. Pooled relative risk (RR) estimates and 95% confidence intervals (CIs) were calculated using random-effects model. In addition, we also estimated RR ratios (RRRs) between men and women. Results: A total of 30 cohort studies contributed to the analysis. The results of the meta-analysis showed that statin users did not experience a significantly decreased risk for developing kidney cancer in both women and men (RR = 1.01, 95% CI = 0.91-1.11). Statin use in women had the reduced tendency for the risk of kidney cancer, but statin use in men had an adverse tendency for the risk of this disease (Women: RR = 0.98, 95% CI = 0.85-1.12; Men: RR = 1.09, 95% CI = 0.99-1.19). The pooled multiple-adjusted women-to-men RRR for incident kidney cancer was 0.90 (95% CI = 0.75-1.05). Compared to non-users, statin users yielded the reduced risk of total, advanced, high-grade, and low-grade prostate cancer by approximately 12%, 18%, 14% and 7% (Total: RR = 0.88, 95% CI = 0.84-0.93; Advanced: RR = 0.82, 95% CI = 0.70-0.95; High-grade: RR = 0.86, 95% CI = 0.68-0.99; Low-grade: RR = 0.93, 95% CI = 0.86-0.99), whereas the significant effects were not observed for bladder cancer (RR = 1.03, 95% CI = 0.88-1.17). Conclusions: The results found that sex difference could affect the association of statin use with the risk of kidney cancer. The statin use could reduce the risk of prostate cancer but no associations were found between statin use and bladder cancer.

Keywords: Statin use, kidney, prostate, bladder, cancer, meta-analysis

Introduction

According to WHO estimates for 2011, cancer now causes more deaths than all coronary heart disease in the United States and throughout the world [1]. Commonly seen urologic cancers such as prostate cancer, kidney cancer, and bladder cancer are leading causes of cancer-related morbidity and mortality globally. Despite rapid advances in early diagnosis and surgical treatment over the past few decades, the numbers of new urologic cancer cases and associated deaths continue to increase, making it become one of the major threats to public health worldwide [2].

To date, the exact cause of urologic cancer remains unclear, and it may involve genetic factors and environmental factors. Certain environmental factors like smoking habit, heavy alcohol intake, high caloric diet and chemical dyes have been identified as potential etiological factors for urologic cancer. However, the fact that only a small portion of individuals exposed to statin use ultimately develop urologic cancer suggests that statin use may play a crucial part in its pathogenesis [3, 4].

The 3-hydroxy-3 methylglutaryl CoA reductase inhibitor (statin), commonly used to treat hypercholesterolemia and prevent coronary heart disease, has recently emerged as anticancer agents because of their antiproliferative, proapoptotic and antimetastatic effects on a variety of cancer cell lines. The previous studies revealed that statins affected lipid raft integrity

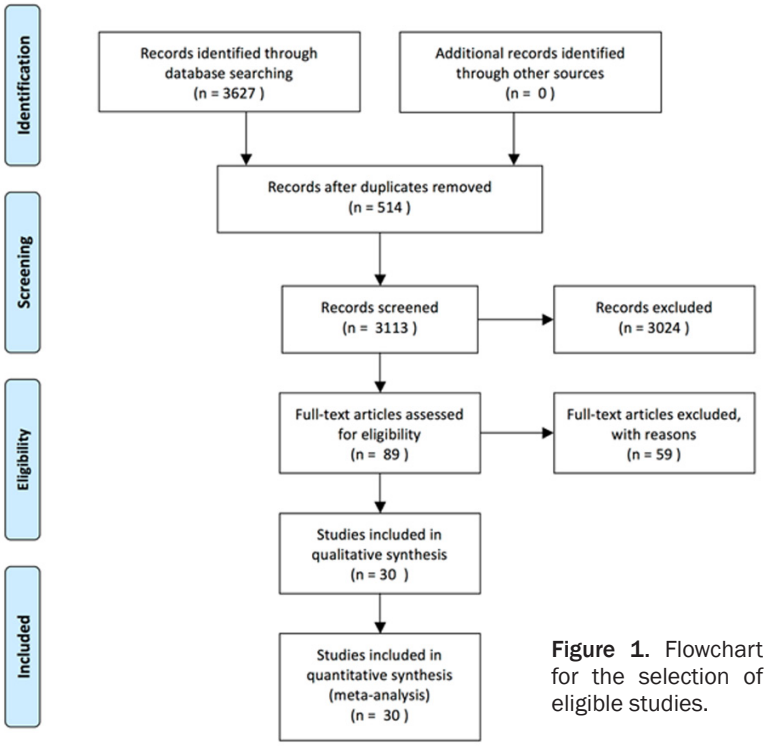

Figure 1. Flowchart for the selection of eligible studies.

on intracellular signaling events downstream of c-Kit by lowering intracellular cholesterol levels [5]. Furthermore, statin profoundly impaired basal and growth factor-stimulated cell growth in vitro and induced apoptosis, indicating the association of statin use with the reduced risk of kidney, bladder and prostate cancer. Recently, many studies investigated the relationship between statin use and the risk of urologic cancer; however, the results of these studies were inconsistent, whether the effect of statin use was controversial during duration remained unclear. In addition, sex-specific associations between statin use and the risk of kidney cancer and bladder cancer have not been definitively determined.

Therefore, we conducted a meta-analysis to pool the results of all available association studies between statin use and the risk of kidney cancer, bladder cancer and prostate cancer. Furthermore, we evaluated women-to-men ratios of RRs for incident kidney cancer.

Materials and methods

Data sources and search strategy

The meta-analysis was evaluated in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (Supplementary.PRISMA). A literature search was performed using the databases of PubMed, MEDLINE, Web of Science to retrieve all relevant studies on the statin use and main urologic cancer published before January, 2017. The search strategy was based on a combination of the terms (hydroxymethylglutaryl-CoA reductase inhibitor or statin or lipid-lowering agent), and (urologic cancer or kidney cancer or bladder cancer or prostate cancer or neoplasm or malignancy). The search was not restricted to any language. In addition, all of the references of relevant reviews and eligibly retrieved articles were also checked. When datasets were insufficient for required data, supplementary data would be checked and the corresponding authors would be contacted for additional information.

Study selection

The inclusion criteria were as follows: 1) cohort studies were published as an original article; 2) the major objective of the studies included in the meta-analysis was to evaluate the association of stain use with risk of urologic cancers; and 3) studies were also required to present the relative risks (RRs) or odds ratios (ORs) or hazard ratios (HRs) with their 95% confidence interval (CI) or sufficient data to calculate these. The exclusion criteria were as follows: 1) repeating publications or duplicates; and 2) insufficient data for analysis.

Two investigators (Jiabi Chen, Bing Zhang) independently reviewed the retrieved records. Any inconsistencies were resolved through consensus with a third author (Wei Zhuang) for adjudication.

Data extraction and study quality assessment

The following characteristics of each of the identified studies were collected independently by two reviewers who used a standardized data extraction form: first author, year of publication,

Table 1. Characteristics of studies included in this meta-analysis of statin use and the risk of kidney, bladder and prostate cancer

Author	Country	Cancer type	Participants (statin users/ non-users)	Study type	Mean Follow-up	Age	Study period	Study quality	Confounders for adjustments
Jacobs et al, 2011	American	Prostate, bladder, kidney cancer	24752/104305	Prospective	NR	> 60	1997-2007	7	Age, sex, race, education, smoking, use of NSAIDs, BMI, physical activity, history of elevated cholesterol, diabetes, heart disease, hypertension
Flick et al, 2007	American	Prostate	22903/46144	Prospective	2.3	56.5	1991-2004	6	Race, diabetes, and Kaiser
Platz et al, 2005	American	Prostate	2847/27796	Prospective	4	63.2	1994-2002	7	Age; body mass index at age 21; height; pack-years of cigarette smoking in the previous decade; first-degree family history of prostate cancer; major ancestry; diabetes; vasectomy; vigorous physical activity; use of aspirin; intakes of total energy, calcium, fructose, α-linolenic acid, tomato sauce, red meat, fish, and alcohol; intake of supplemental zinc; and high intake of vitamin E.
Sato et al, 2006	Japan	Prostate, bladder, kidney cancer	179/84	Retrospective	NR	NR	1991-1995	6	Age, sex, total serum cholesterol level, smoking
Friis et al, 2005	Denmark	Prostate	12251/321246	Retrospective	3.3	46.4	1989-2002	7	Age, gender, calendar period and use of NSAID, HRT and cardiovascular drugs
Lovastatin Study Groups et al, 1993	American, Canada, Finland	Prostate	NR/NR	Retrospective	4.8	NR	NR	6	Age, sex
Friedman et al, 2008	American	Prostate, bladder, kidney cancer	361859/3881208	Retrospective	4.91	NR	1994-2003	8	Calendar year
Boudreau et al, 2008	American	Prostate	12013/71359	Retrospective	3.3	57.6	1990-2005	6	Age, diabetes, hypercholesterolemia, other lipid lowering drug use, and NSAID use
Smeeth et al, 2008	UK	Prostate	129288/600241	Retrospective	4.4	40 +	1995-2006	7	Age, sex, propensity score, year of index date, first diagnosis of any of the following post-index date: diabetes, cerebrovascular disease, coronary heart disease, peripheral vascular disease, other atheroma, atrial fibrillation, heart failure, hyperlipidemia, hypertension, other circulatory disease, cancer, dementia, first use of any of the following post-index date: aspirin, nitrates, fibrates, b-blockers, calcium channel blockers, potassium channel activators, diuretics, positive inotropes, anticoagulants, antihypertensive, or other cardiovascular drugs.
Haukka et al, 2010	Finland	Prostate, bladder cancer	472481/472481	Retrospective	3.1	60	1996-2005	8	Age, sex, follow-up period
Murtola et al, 2010	Finnish	Prostate	6692/16516	Retrospective	6.9	56.3	1996-2004	6	Age, family history of prostate cancer, use of aspirin, antidiabetic drugs and/or antihypertensive drugs, number of PSA screens and calendar period of screening.
Nordstrom et al, 2015	Sweden	Prostate	4825/11923	Retrospective	NR	61.2	2007-2012	6	Age, natural log-transformed prostate specific antigen (PSA) concentration, PSA quotient, educational level, use of aspirin, use of statin and use of antidiabetic medication.

Platz et al, 2014	American	Prostate	2249/7208	Prospective	NR	63.3	1994-2003	7	Age
Farwell et al, 2011	England	Prostate	41079/14797	Retrospective	5.6	65.7	1997-2007	6	Age, statin use, finasteride use history, serum total cholesterol, race, smoking history, aspirin use, heart disease, diabetes mellitus, history of prostate-specific antigen test
Tan et al, 2010	AMERICAN	Prostate	1022/3182	Retrospective	NR	64.2	2000-2007	6	Age, BMI, African-American race, DRE, prostate volume and number of cores surveyed
Hippisley-Cox et al, 2010	UK	Prostate, kidney cancer	225922/1778770	Prospective	1.5	44.4	2002-2008	7	Age, sex, comorbidity score, BMI, use of NSAID, smoking, hypertension, use of hormones
Freedland et al, 2013	American	Prostate cancer	NR/NR	Prospective	4	62.9	NR	8	Age, race, baseline PSA, prostate volume, body mass index (BMI), comorbidities, smoking, alcohol intake and treatment arm
Kantor et al, 2015	American	Prostate cancer	4503/27558	Prospective	5.2	57.2	2002-2009	8	Age, race/ethnicity, enrollment source, household income, insurance coverage, time since last doctor visit, history of prostate specific-antigen screening, history of digital rectal exam, history of high cholesterol, and family history of prostate cancer.
Lustman et al, 2014	Israel	Prostate cancer	37645/29096	Retrospective	NR	58	NR	7	Age, DM, BMI, CVD and smoker
Karp et al, 2008	CaNRda	Prostate, bladder, kidney cancer	11338/18738	Retrospective	NR	69.6	1998-2004	6	Age, sex, marital status, comorbidities, use of non-statin cardiac medications, in-hospital procedure performed, length of hospital stay, calendar year, specialty of the treating physician, area of location, and annual volume of admissions
Chen et al, 2015	Taiwan	Prostate	8861/53037	Retrospective	NR	40.3	2000-2008	6	Age, sex, comorbidity condition, non- statin lipid-lowering drugs, aspirin, acetylcholinesterase (ACE) inhibitors, area, index year, and anti-HBV drug
Matsushita et al, 2010	Japan	Prostate	7375/6349	Prospective	4.7	57.9	NR	7	Age, sex, smoking habit
Leung et al, 2013	Taiwan	Prostate, bladder cancer	6841/27364	Prospective	NR	61.5	NR	6	Age, sex, and whether using other lipid-lowering agents
Chen-Pin et al, 2014	American	Prostate	NR/NR	Retrospective	6.4	66.9	2003-2013	6	Age, baseline HbA1c, and comorbidities
Chan et al, 2012	American	Prostate	1377/3692	Prospective	NR	73.1	2000-20087	7	Age, study site, race, body mass index, marital status, family history of prostate cancer, number of comorbidities, physical activity, and smoking history.
Fowke et al, 2011	American	Prostate	783/1365	Retrospective	NR	65.1	2002-2010	7	Age, race, biopsy outcome (all only), family history, BMI, WHR, prostate volume, PSA levels, aspirin use, treatment for diabetes, BPH, or CVD
Breau et al, 2010	American	Prostate	634/1813	Retrospective	15.7	55.8	1990-2007	6	Age, comorbidities, use of NSAIDs, 5-α reductase inhibitors, and α-blockers.
Morote et al, 2014	Mediterrnean	Prostate	744/1664	Retrospective	NR	57.2	2006-2011	6	Age, sex
Marelli et al, 2011	American	Prostate, bladder, kidney cancer	45857/45857	Retrospective	4.6	69.8	1990-2009	7	Age, sex, smoking status, duration of observation window, propensity score, LDL levels,
Liu et al, 2012	China	Kidney cancer	22208/78722	Prospective	NR	67.7	1990-2008	6	Age, smoking, body mass index, history of hypertension, history of diabetes, physical activity, fruit intake, vegetable intake, alcohol intake, and duration of regular non-aspirin NSAIDs use, and parity.

NR: not reported.

number of subjects and number of lung cancer cases, study period, country of the population studied, study design, mean follow-up time, average age. We extracted the RR estimates that reflected the greatest degree of control for potential confounders.

The quality of each study was assessed independently by two authors by using the Newcastle-Ottawa Scale (NOS), which used a 'star system' to evaluate data quality [6]. The NOS criteria includes three broad perspectives-the selection, comparability and outcome, and the scores range from 0 (worst) to 9 (best). A score of 5 or greater was considered high quality, where scores less than 4 were considered low quality. Any discrepancies were settled by a joint revaluation of the original article through consensus.

Statistical analysis

The RR with 95% CI was a commonly used measure of effect of interest in the medical. ORs were converted into RRs using the following formula: $RR = OR/[(1-P_0) + (P_0 \times OR)]$, where P_0 stands for the incidence of urologic cancers in the non-statin use group. A random-effects model or fixed-effects model was performed in the meta-analysis depend on degree of heterogeneity. The heterogeneity among individual studies was evaluated by calculating the Cochran's Q statistic ($P < 0.10$ suggesting statistically significance). Fixed-effects models were chosen to pool risk estimates when heterogeneity among studies was considered statistically insignificant. Otherwise, random-effects model was used to combine the results. Subgroup analysis was conducted based on study design (Prospective studies v. Retrospective studies), types of statins (Simvastatin v. Lovastatin v. Pravastatin v. Fluvastatin v. Atorvastatin v. Rosuvastatin), and duration of statin use (Long-term or Short-term). The meta-regression and sensitivity analyses also were evaluated to explore the potential sources of heterogeneity between studies. In addition, we selected cohort studies stratified by gender with RR and computed the women-to-men ratios of RRs (RRR) with 95% confidence intervals (CI). These RRRs were estimated for the comparison of current statin user with non-users, separately for studies with the maximum adjustment variables [7]. Publication bias was detected using Begg's test and Egger's test [8]. We used STATA version 11.0 (Stata Corp LP, College Station, TX, USA) to conduct all statistical analyses. Statistical significance was determined using the two-tailed test, where $P < 0.05$ was considered significant, and in Egger's linear regression and Begg's rank correlation, a level of 0.10 was used.

Results

A total of 3627 articles were identified during the initial search. After employing exclusion criteria, 89 potentially relevant studies were eligible for further review. After reviewing the full-text articles, 30 were included in this meta-analysis (**Figure 1**) [9-38].

The main characteristics of the studies were described in **Table 1.** Among the 30 cohort studies, eleven studies were prospective cohort studies, and 19 studies were retrospective cohort studies. The number of subjects included 9226757 participants, ranging from 263 to 4243067. Among these studies, 29 studies assessed the association of statin use with the risk of prostate cancer, eight were bladder cancer, seven studies were kidney cancer. Of 30 included studies, sixteen studies were conducted in America, seven studies were conducted in Europe, seven studies were conducted in Asia. The average age of the subjects ranged from 40.3 to 73.1 years. Participants were followed-up for 1.5 to 15.7 years. All studies were all considered high quality, indicating the quality of included studies was generally good. Most of the studies were adjusted for age (n = 28), whereas a fewer number of adjusted for gender (n = 9), race (n = 5), body mass index (n = 7), smoking (n = 8) and use of NSAIDs (n = 6).

Statins and risk of kidney cancer.

The relationship between statin use and risk of kidney cancer was evaluated in seven studies. Among these studies, one studies showed significant associations of statin use with risk of kidney cancer, and significant associations were not observed in six studies. The results of the present meta-analysis showed that statin users did not experience a significantly decreased risk for developing kidney cancer in both women and men (RR = 1.01, 95% CI = 0.91-1.11; $I^2 = 45.9\%$; **Figure 2**). The results of the stratified analysis found that study design

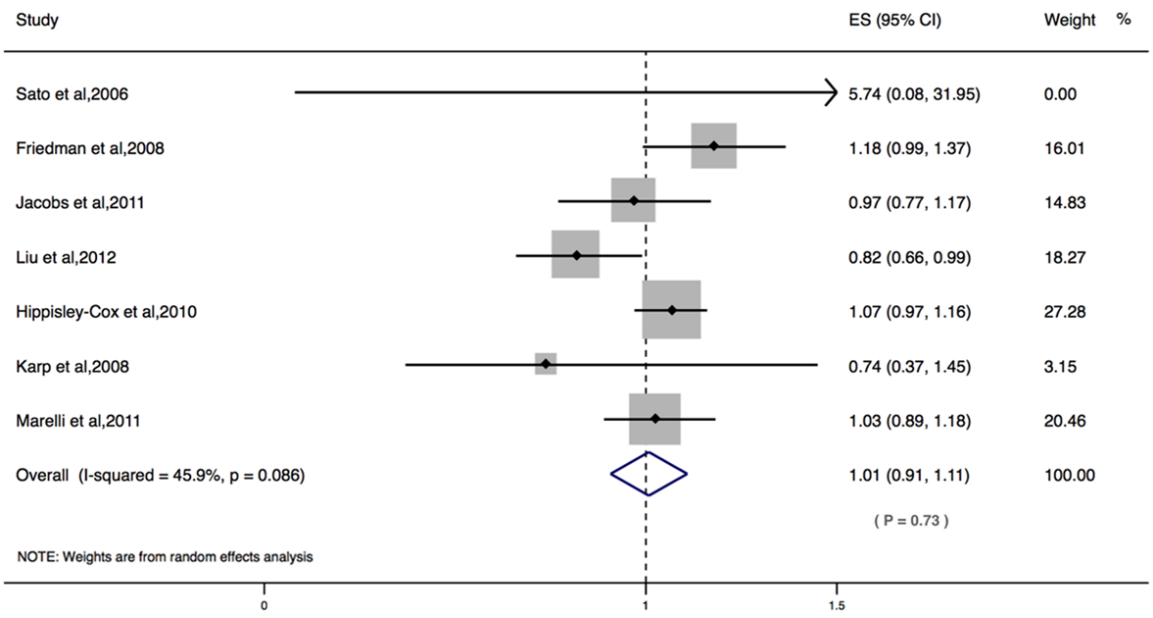

Figure 2. Forest plot on the associations between statin use and the risk of kidney cancer.

did not alter the association of statin use with the risk of kidney cancer (Prospective studies: RR = 0.95, 95% CI = 0.89-1.01; Retrospective studies: RR = 0.91, 95% CI = 0.69-1.13; **Table 2**). This research provided no evidence to suggest that long-term statin use was beneficial for the prevention of kidder cancer (RR = 0.98, 95% CI = 0.78-1.18). No publication bias was observed among studies using Begg's *P* value (P = 0.76) and Egger's test (P = 0.72) (**Figure 3A**).

Subsequently, we explored on the sex-specific associations between statin use and the risk of kidney cancer. Four studies provided RRs for the associations of statins and this disease risk in men and women, respectively.

The pooled multiple-adjusted women-to-men RRR for incident kidney cancer was 0.90 (95% CI 0.75, 1.05) (**Figure 4**). Statin use in women had the reduced tendency for the risk of kidney cancer, but statin use in men had an adverse tendency for the risk of this disease (Women: RR = 0.98, 95% CI = 0.85-1.12; Men: RR = 1.09, 95% CI = 0.99-1.19).

Statins and risk of prostate cancer.

The relationship between statin use and risk of prostate cancer was evaluated in 29 studies. Among these studies, eighteen studies did not show significant associations of statin use with risk of prostate cancer, significant associations of statin use with reduced risk of prostate cancer were observed in ten studies, and one study found that statin use could increase the risk of prostate cancer. When all included studies were pooled into the meta-analysis, the results showed that statin users experienced a significantly decreased risk for developing prostate cancer (RR = 0.88, 95% CI = 0.84-0.93; I^2 = 87.9%, P < 0.001; **Figure 5**), especially for long-term statin use (RR = 0·72, 95% CI: 0·60-0·83). The study design could not significantly alter the risk of prostate cancer (Prospective studies: RR = 0.94, 95% CI = 0.89-0.99; retrospective studies: RR = 0.85, 95% CI = 0.78-0.91). The results of subgroup analysis showed that the use of statins is beneficial for the prevention of advanced prostate cancer (RR = 0.82, 95% CI = 0.70-0.95), high-grade prostate cancer (RR = 0.86, 95% CI = 0.68-0.99) or low-grade prostate cancer (RR = 0.93, 95% CI = 0.86-0.99). The subgroup results based on statin types shared consistency in the direction of the effect (Pravastatin: RR = 0.99, 95% CI = 0.97-1.02; Simvastatin (RR = 0.86, 95% CI = 0.61-1.12; Fluvastatin: RR = 0.86, 95% CI = 0.68-0.99; Atorvastatin: RR = 0.89, 95% CI = 0.68-1.10; Rosuvastatin: RR = 0.58, 95% CI = 0.17-1.34; Lovastatin: RR = 0.94, 95% CI = 0.93-0.96). The sensitivity analysis by removing one study at a time showed the robustness

Table 2. Overall effect estimates for urologic cancers and statin use according to study characteristics

Subgroup	N	OR	Lower	Upper	Q	P	I^2	Begg	Egger
Prostate cancer									
Total	29	0.88	0.84	0.93	232.66	< 0.001	87.90%	0.30	0.11
Advanced prostate cancer	8	0.82	0.70	0.95	14.44	0.044	51.50%	1.00	0.67
High grade prostate cancer	13	0.86	0.68	0.99	81.92	< 0.001	85.40%	0.58	0.41
Low grade prostate cancer	9	0.93	0.86	0.99	14.48	0.07	44.80%	0.60	0.98
Ever statin use	4	0.91	0.86	0.96	0.43	0.934	0.00%	0.73	0.25
Long-term statin use (≥ 3 years)	10	0.85	0.55	1.15	392.89	< 0.001	97.70%	0.09	0.37
Short-term statin use (< 3 years)	2	0.72	0.60	0.83	0.35	0.838	0.00%	1.00	0.51
Stain types									
Lipophilic	3	0.76	0.34	1.17	83.5	< 0.001	97.60%	0.30	0.38
Hydrophilic	3	0.99	0.63	1.42	10.68	0.005	81.30%	1.00	0.49
Simvastatin	5	0.86	0.61	1.12	476.77	< 0.001	99.00%	0.71	0.39
Lovastatin	3	0.94	0.93	0.96	2.59	0.274	22.80%	0.30	0.20
Pravastatin	5	0.99	0.97	1.02	5.45	0.244	26.60%	1.00	0.36
Fluvastatin	4	0.99	0.97	1.02	1.11	0.775	0.00%	0.73	0.68
Atorvastatin	5	0.89	0.68	1.10	69.17	< 0.001	92.80%	0.45	0.36
Rosuvastatin	2	0.58	0.17	1.34	9.54	0.002	89.50%	1.00	NA
Study design									
Prospective	10	0.94	0.89	0.99	333.04	0.1	38.70%	0.41	0.13
Retrospective	19	0.85	0.78	0.91	14.67	< 0.001	94.60%	0.22	0.45
Bladder cancer									
Total	8	1.03	0.88	1.17	29.59	< 0.001	76.30%	0.54	0.35
Long-term statin use (≥ 3 years)	3	1.30	0.91	1.69	10.41	0.015	71.20%	1	0.77
Pravastatin	2	1.03	0.96	1.10	1.78	0.182	43.80%	1	NA
Study design									
Prospective	2	0.87	0.67	1.06	10.37	< 0.001	90.40%	0.32	0.27
Retrospective	6	0.89	0.79	0.99	117.35	< 0.001	95.70%	0.64	0.45
Kidder cancer									
Total	7	1.01	0.91	1.11	11.09	0.086	45.90%	0.76	0.72
Long-term statin use (≥ 3 years)	3	0.98	0.78	1.18	3.47	0.483	0.00%	0.46	0.36
Study design									
Prospective	3	1.04	0.96	1.11	3.03	0.234	34.00%	0.44	0.35
Retrospective	4	0.91	0.69	1.13	108.28	< 0.001	97.20%	0.18	0.21

of our findings. In addition, no publication bias was observed among studies using Begg's *P* value (P = 0.30) and Egger's test (P = 0.11) (**Figure 3B**).

Statins and risk of bladder cancer

Subsequently, we assessed the relationship between statin use and risk of bladder cancer in eight studies. Among them, one studies showed a significantly reduced risk of bladder cancer, two studies showed a significantly increased risk of this disease and five studies reported no significant associations. The results of the present analysis revealed that bladder cancer risk did not yield statistically significant benefit from statin use (RR = 1.03, 95% CI = 0.88-1.17; **Figure 6**). The results of the stratified analysis found that study design did not alter the tendency of association of statin use with the risk of bladder cancer (Prospective studies: RR = 0.87, 95% CI = 0.67-1.06; Retrospective studies: RR = 0.89, 95% CI = 0.79-0.99). The results of the stratified analysis found that pravastatin did not show a significantly decreased risk for developing bladder cancer (RR = 1.03, 95% CI = 0.96-1.10). In addition, the sensitivity analysis found that the significant relationships in the pooled RRs remained stable. The Begg's test and Egger's

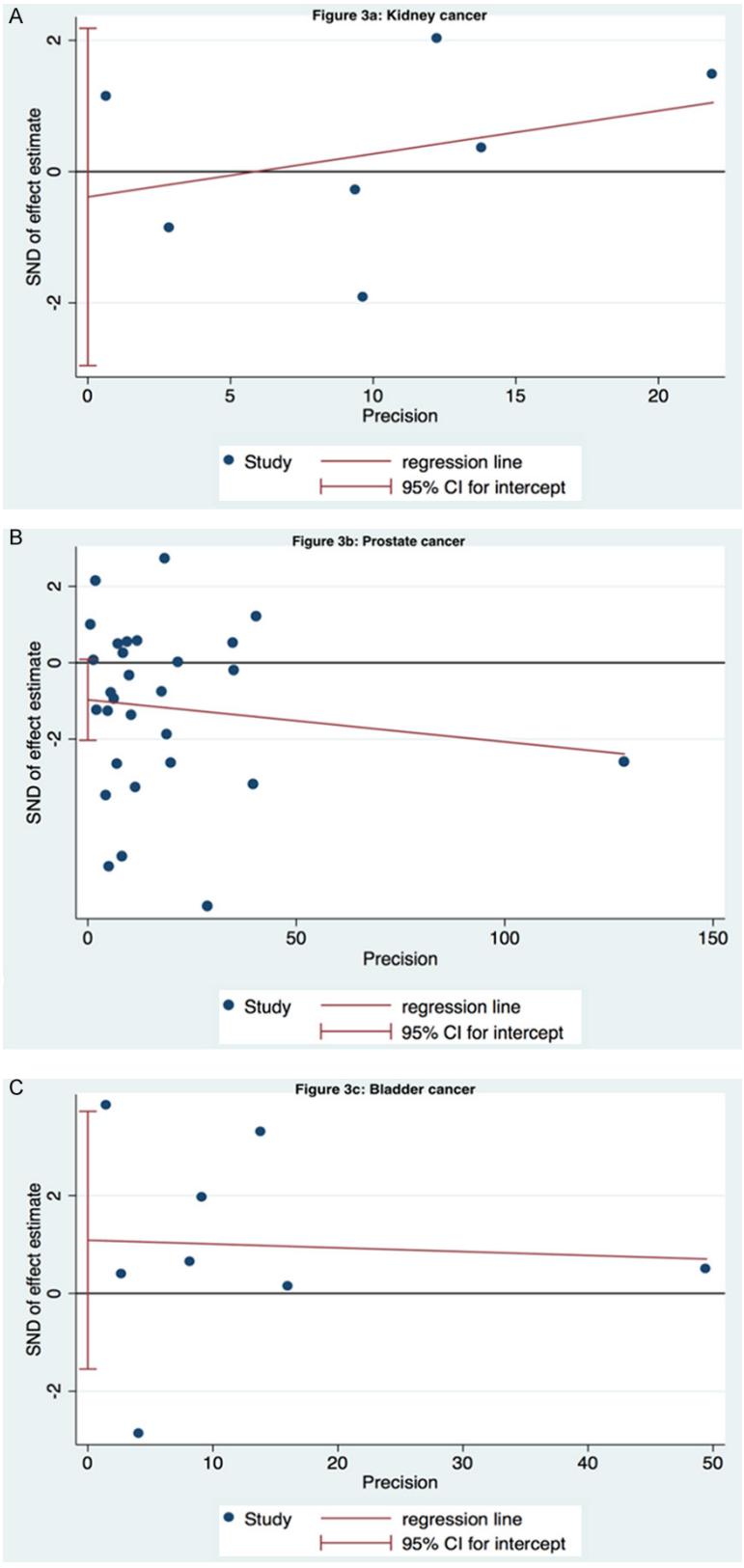

Figure 3. Egger's publication bias plot for the association between statin use and the risk of kidney cancer, prostate cancer and bladder cancer.

regression test did not find any evidence for the presence of publication bias in the eligible studies (both P > 0.1; **Figure 3C**).

Discussion

The previous meta-analyses conducted by Nayan et al [39] included both RCTs and observational studies demonstrated that statin use was not associated with the risk of kidney cancer. In line with this meta-analyses, the present meta-analysis did not appreciably show the association with the risk for kidney cancer among statin users as compared to non-users in both men and women. However, there was a significant heterogeneity among the included studies (P < 0.001). The meta-regression and subgroup analysis did find that sex difference might account for the source of heterogeneity. Compared to non-users, statin use in men had an adverse tendency for the risk of kidney cancer, but statin use in women showed the beneficial tendency for the risk of kidney cancer. In agreement with our results, the previous cohort study by Friedman et al demonstrated that use of statins in men would increase 23% risk of kidney cancer (RR = 1.23, 95% CI = 1.02-1.48), and the large prospective studies by Liu et al found that statin use could reduce marginally the 32% risk of this disease among women (RR = 0.68, 95% CI = 0.46-1.00) [14, 38]. In addition, the pooled multiple-adjusted women-to-men RRR in our meta-analysis might provide the potential evidence of sex difference in the effect

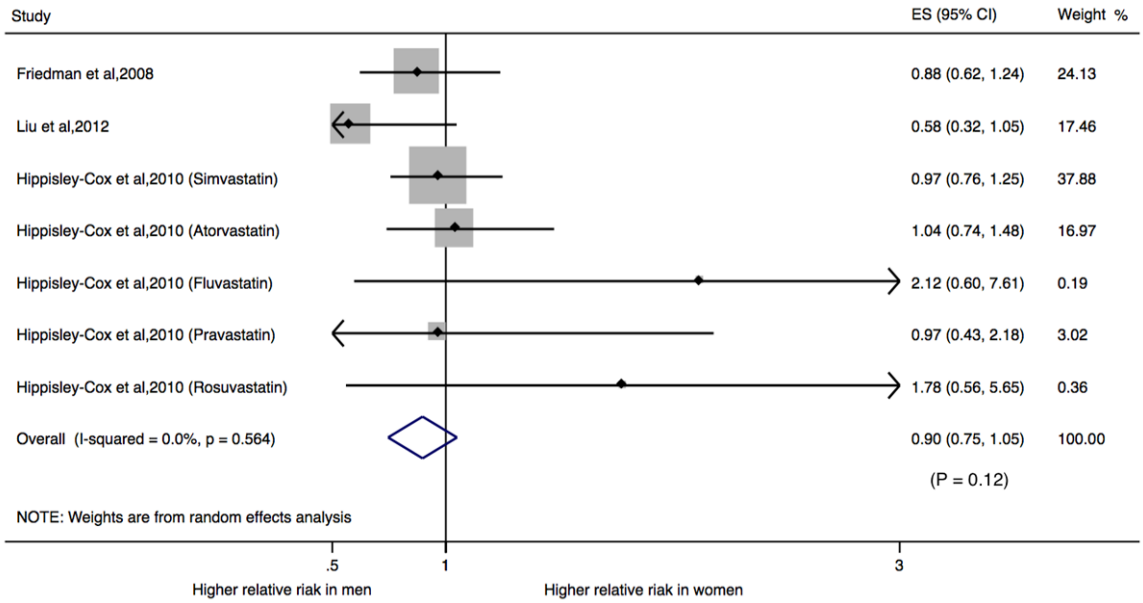

Figure 4. Relative risk ratios (RRR) of sex differences (female to male) for the association between statin use and the risk of kidney cancer.

of statin use on risk of kidney cancer which indicating further studies to evaluate the potential effect of statin use on risk of kidney cancer should take sex disparities into account [40]. However, the findings of this meta-analysis suggested that there was no association between statin use and risk of bladder cancer. Due to limited data, we did not explore the sex difference in the relationship between statin use and the risk of bladder cancer.

We found significantly the reduced risk of total, advanced, high-grade, and low-grade prostate cancer among statin users as compared to non-users by approximately 12%, 18%, 14% and 7%, respectively. In our subgroup analyses, we observed a significant protective association of short-term statin use with the reduced risk of prostate cancer, in contrast with the absent association between long-term statin use and risk of prostate cancer, indicating the duration of statin use might show a significant association with its efficacy.

Although there was a decreased risk of low grade prostate cancer with a borderline significance, either residual confounding or type I error of studies could partially account for this reason. In addition, the irregular use of statins in many participants and various definitions of duration of exposure could was the possible explanation [41]. Therefore, the cumulative amount of statin defined daily doses might be small despite the long duration use. It should be noted that the inverse association between the risk of prostate cancer and statin use was dose-dependent with a cumulative amount of statin use [41-43]. Therefore, future studies should take fully into account of effect of cumulative amount of defined daily doses on the overall statins exposure.

The present meta-analysis had several strengths. The present review includes a large number of people from different studies. Almost the included studies had adjusted for age and smoking in the analyses and most of the studies had a high quality which gave more reliable assessment of the relation between statin use and risk of prostate cancer. Additionally, the association was essentially consistent among subgroups stratified by characteristics of participants, indicating that the conclusions of the present study were not dependent on arbitrary decisions in the present meta-analysis. Finally, the present results were unlikely to be altered significantly from publication bias, as indicated by the funnel plots and other analyses.

Some potential limitations of the present study should also merit consideration in interpreting the findings. First, although the present results showed that statin use might significantly

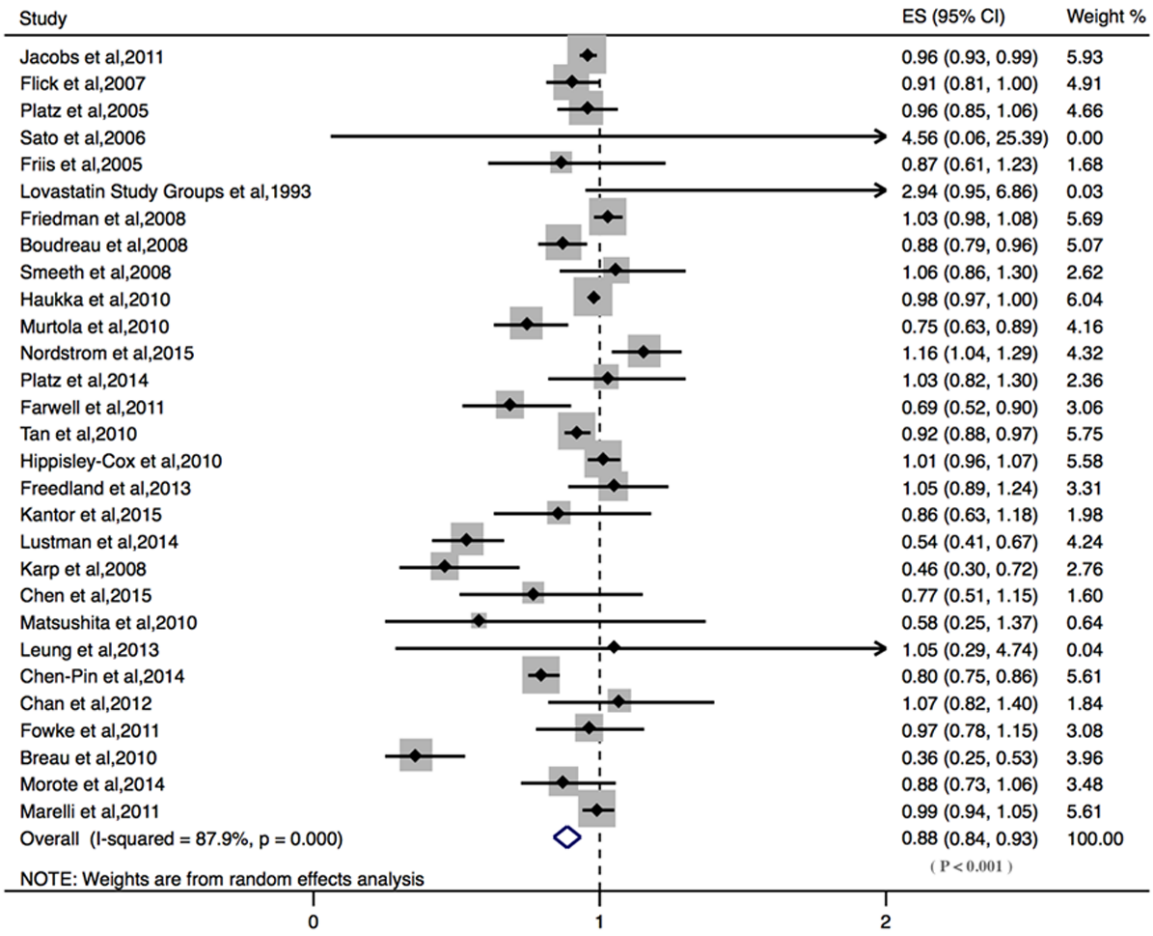

Figure 5. Forest plot on the associations between the statin use and the risk of prostate cancer.

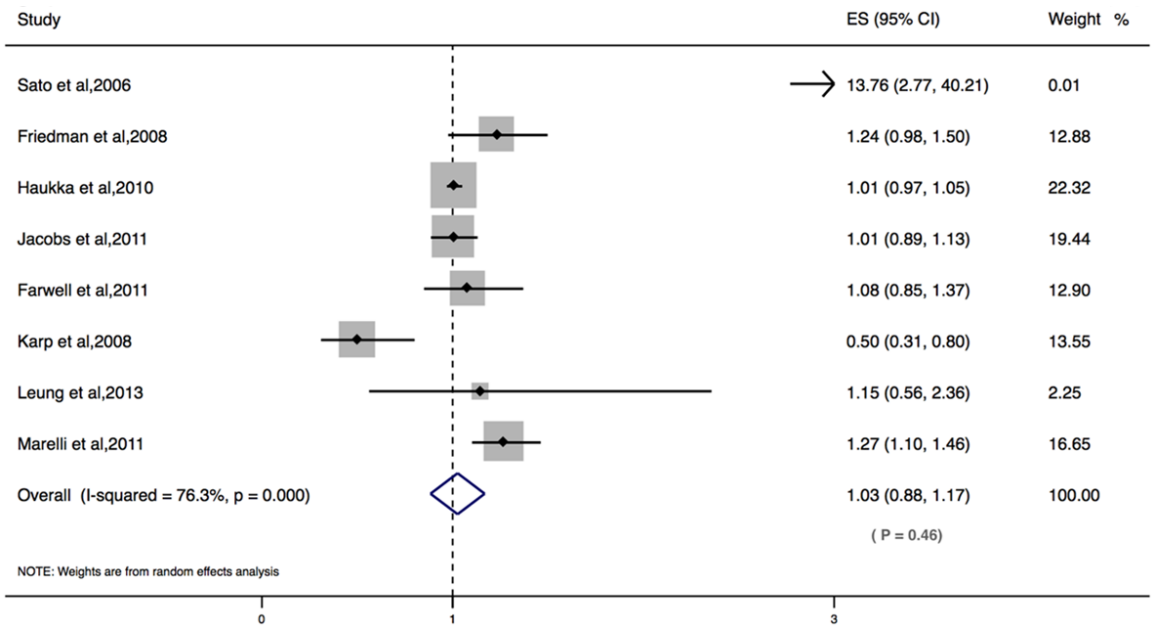

Figure 6. Forest plot on the associations between the statin use and the risk of bladder cancer.

reduce the risk of prostate cancer, especially for short-term statin use, and the present study was based on observational studies and might have the problems of potential bias and confounding effects associated with such studies, however, the combined sample size was relatively large, and the present results remained robust, adding to the strength of this analysis. Second, even though several confounding factors had been adjusted in all the studies incorporated, the possibility of other uncontrolled or potential residual confounding could not be fully excluded in the present meta-analysis, which might have led to underestimation or overestimation of the association. Third, both the environmental factors and genetic factors likely affected the risk of prostate cancer, which might also partly influence our results. Our analysis was based primarily on data and information provided from the original literature; however, the included studies did not control for these confounding factors or report sufficient data to analyze the association between statin use and lung cancer risk adjusted for different environmental factors and genes. Thus, the assessment of potential gene-gene or gene-environment interactions was limited, and the possibility that environmental factors and other genes might affect the lung cancer risk interactively that could not be excluded in the present study. Further large research studies that allowed for the adjustment by these covariates, including genes and environmental factors, should be conducted. Finally, as with any meta-analysis, the potential for publication bias was a concern. Despite no publication bias examined in the present study, it was still difficult to fully rule out such bias because there was not a sufficient number of studies to detect it adequately.

In conclusion, the present meta-analysis found that statin use in men had an adverse tendency for the risk of kidney cancer compared to nonusers, but statin use in women showed the beneficial tendency for the risk of this disease. However, statin use was significantly associated with a decrease in the risk of developing prostate cancer, whereas the significant effects were not observed for bladder cancer. Moreover, a plausible association of a decreased risk of advanced, high-grade and low-grade with statin use was also found. It should also be noted that there are only a few prospective studies that have examined this association, which limited the power of meta-analysis. Therefore, further well-designed large studies with prospective cohort design, especially according to sex difference are required before definitive conclusions can be drawn regarding the potential effect of statin use on the risk of bladder and kidney cancer.

Disclosure of conflict of interest

None.

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References

[1] Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin 2015; 65: 87-108.

[2] Shirk JD, Tan HJ, Hu JC, Saigal CS, Litwin MS. Patient experience and quality of urologic cancer surgery in US hospitals. Cancer 2016; 122: 2571-2578.

[3] Nielsen SF, Nordestgaard BG, Bojesen SE. Statin use and reduced cancer-related mortality. N Engl J Med 2013; 368: 576-577.

[4] Peto R, Emberson J, Landray M, Baigent C, Collins R, Clare R, Califf R. Analyses of cancer data from three ezetimibe trials. N Engl J Med 2008; 359: 1357-1366.

[5] Mullen PJ, Yu R, Longo J, Archer MC, Penn LZ. The interplay between cell signalling and the mevalonate pathway in cancer. Nat Rev Cancer 2016; 16: 718-731.

[6] Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. Available online: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp (accessed on 10 June 2016).

[7] Huxley RR, Woodward M. Cigarette smoking as a risk factor for coronary heart disease in women compared with men: a systematic review and meta-analysis of prospective cohort studies. Lancet 2011; 378: 1297-1305.

[8] Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta- analysis detected by a simple, graphical test. BMJ 1997; 315: 629-634.

[9] Platz EA, Leitzmann MF, Visvanathan K, Rimm EB, Stampfer MJ, Willett WC, Giovannucci E. Statin drugs and risk of advanced prostate

cancer. J Natl Cancer Inst 2006; 98: 1819-1825.
[10] Flick ED, Habel LA, Chan KA, Van Den Eeden SK, Quinn VP, Haque R, Orav EJ, Seeger JD, Sadler MC, Quesenberry CP Jr, Sternfeld B, Jacobsen SJ, Whitmer RA, Caan BJ. Statin use and risk of prostate cancer in the California Men's Health Study cohort. Cancer Epidemiol Biomarkers Prev 2007; 16: 2218-1125.
[11] Lovastatin Study Groups I Through IV. Lovastatin 5-year safety and efficacy study. Arch Intern Med 1993; 153: 1079-1087.
[12] Friis S, Poulsen AH, Johnsen SP, McLaughlin JK, Fryzek JP, Dalton SO, Sørensen HT, Olsen JH. Cancer risk among statin users: a population-based cohort study. Int J Cancer 2005; 114: 643-647.
[13] Sato S, Ajiki W, Kobayashi T, Awata N; PCS Study Group. Pravastatin use and the five-year incidence of cancer in coronary heart disease patients: from the prevention of coronary sclerosis study. J Epidemiol 2006; 16: 201-206.
[14] Friedman GD, Flick ED, Udaltsova N, Chan J, Quesenberry CP Jr, Habel LA. Screening statins for possible carcinogenic risk: up to 9 years of follow-up of 361,859 recipients. Pharmacoepidemiol Drug Saf 2008; 17: 27-36.
[15] Haukka J, Sankila R, Klaukka T, Lonnqvist J, Niskanen L, Tanskanen A, Wahlbeck K, Tiihonen J. Incidence of cancer and statin usage--record linkage study. Int J Cancer 2010; 126: 279-284.
[16] Hippisley-Cox J, Coupland C. Unintended effects of statins in men and women in England and Wales: population based cohort study using the QResearch database. BMJ 2010; 340: c2197.
[17] Jacobs EJ, Newton CC, Thun MJ, Gapstur SM. Long-term use of cholesterol-lowering drugs and cancer incidence in a large United States cohort. Cancer Res 2011; 71: 1763-1771.
[18] Chen CI, Kuan CF, Fang YA, Liu SH, Liu JC, Wu LL, Chang CJ, Yang HC, Hwang J, Miser JS, Wu SY. Cancer risk in HBV patients with statin and metformin use: a population-based cohort study. Medicine 2015 ; 94: e462.
[19] Karp I, Behlouli H, Lelorier J, Pilote L. Statins and cancer risk. Am J Med 2008; 121: 302-309.
[20] Leung HW, Chan AL, Lo D, Leung JH, Chen HL. Common cancer risk and statins: a population-based case-control study in a Chinese population. Expert Opin Drug Saf 2013; 12: 19-27.
[21] Matsushita Y, Sugihara M, Kaburagi J, Ozawa M, Iwashita M, Yoshida S, Saito H, Hattori Y. Pravastatin use and cancer risk: a meta-analysis of individual patient data from long-term prospective controlled trials in Japan. Pharmacoepidemiol Drug Saf 2010; 19: 196-202.
[22] Marelli C, Gunnarsson C, Ross S, Haas S, Stroup DF, Cload P, Clopton P, DeMaria AN. Statins and risk of cancer: a retrospective cohort analysis of 45,857 matched pairs from an electronic medical records database of 11 million adult Americans. J Am Coll Cardiol 2011; 58: 530-537.
[23] Smeeth L, Douglas I, Hall AJ, Hubbard R, Evans S. Effect of statins on a wide range of health outcomes: a cohort study validated by comparison with randomized trials. Br J Clin Pharmacol 2009; 67: 99-109.
[24] Boudreau DM, Yu O, Buist DS, Miglioretti DL. Statin use and prostate cancer risk in a large population-based setting. Cancer Causes Control 2008; 19: 767-774.
[25] Murtola TJ, Tammela TL, Määttänen L, Huhtala H, Platz EA, Ala-Opas M, Stenman UH, Auvinen A. Prostate cancer and PSA among statin users in the Finnish prostate cancer screening trial. Int J Cancer 2010; 127: 1650-1659.
[26] Nordström T, Clements M, Karlsson R, Adolfsson J, Grönberg H. The risk of prostate cancer for men on aspirin, statin or antidiabetic medications. Eur J Cancer 2015; 51: 725-733.
[27] Platz EA, Tangen CM, Goodman PJ, Till C, Parnes HL, Figg WD, Albanes D, Neuhouser ML, Klein EA, Lucia MS, Thompson IM Jr, Kristal AR. Statin drug use is not associated with prostate cancer risk in men who are regularly screened. J Urol 2014; 192: 379-384.
[28] Farwell WR, D'Avolio LW, Scranton RE, Lawler EV, Gaziano JM. Statins and prostate cancer diagnosis and grade in a veterans population. J Natl Cancer Inst 2011; 103: 885-892.
[29] Tan N, Klein EA, Li J, Moussa AS, Jones JS. Statin use and risk of prostate cancer in a population of men who underwent biopsy. J Urol 2011; 186: 86-90.
[30] Freedland SJ, Hamilton RJ, Gerber L, Banez LL, Moreira DM, Andriole GL, Rittmaster RS. Statin use and risk of prostate cancer and high-grade prostate cancer: results from the REDUCE study. Prostate Cancer Prostatic Dis 2013; 16: 254-259.
[31] Kantor ED, Lipworth L, Fowke JH, Giovannucci EL, Mucci LA, Signorello LB. Statin use and risk of prostate cancer: results from the southern community cohort study. Prostate 2015; 75: 1384-1393.
[32] Lustman A, Nakar S, Cohen AD, Vinker S. Statin use and incident prostate cancer risk: does the statin brand matter? A population-based cohort study. Prostate Cancer Prostatic Dis 2014; 17: 6-9.
[33] Chen-Pin W, Javier H, Lorenzo C, Downs JR, Thompson IM, Pollock B, Lehman D. Statins and finasteride use differentially modify the impact of metformin on prostate cancer inci-

dence in men with type 2 diabetes. Ann Transl Med Epidemiol 2014; 1. pii: 1004.
[34] Chan JM, Litwack-Harrison S, Bauer SR, Daniels NA, Wilt TJ, Shannon J, Bauer DC. Statin use and risk of prostate cancer in the prospective osteoporotic fractures in men (MrOS) study. Cancer Epidemiol Biomarkers Prev 2012; 21: 1886-1888.
[35] Fowke JH, Motley SS, Barocas DA, Cookson MS, Concepcion R, Byerly S, Smith JA Jr. The associations between statin use and prostate cancer screening, prostate size, high-grade prostatic intraepithelial neoplasia (PIN), and prostate cancer. Cancer Causes Control 2011; 22: 417-426.
[36] Breau RH, Karnes RJ, Jacobson DJ, McGree ME, Jacobsen SJ, Nehra A, Lieber MM, St Sauver JL. The association between statin use and the diagnosis of prostate cancer in a population based cohort. J Urol 2010; 184: 494-499.
[37] Morote J, Celma A, Planas J, Placer J, de Torres I, Olivan M, Carles J, Reventós J, Doll A. Role of serum cholesterol and statin use in the risk of prostate cancer detection and tumor aggressiveness. Int J Mol Sci 2014; 15: 13615-13623.
[38] Liu W, Choueiri TK, Cho E. Statin use and the risk of renal cell carcinoma in 2 prospective US cohorts. Cancer 2012; 118: 797-803.
[39] Nayan M, Punjani N, Juurlink DN, Finelli A, Austin PC, Kulkarni GS, Uleryk E, Hamilton RJ. Statin use and kidney cancer survival outcomes: a systematic review and meta-analysis. Cancer Treat Rev 2017; 52: 105-116.
[40] Peters SA, Huxley RR, Woodward M. Diabetes as risk factor for incident coronary heart disease in women compared with men: a systematic review and meta-analysis of 64 cohorts including 858,507 individuals and 28,203 coronary events. Diabetologia 2014; 57: 1542-1551.
[41] Bansal D, Undela K, D'Cruz S, Schifano F. Statin use and risk of prostate cancer: a meta-analysis of observational studies. PLoS One 2012; 7: e46691.
[42] Zhang Y, Zang T. Association between statin usage and prostate cancer prevention: a refined meta-analysis based on literature from the years 2005-2010. Urol Int 2013; 90: 259-262.
[43] Luo Y, She DL, Xiong H, Fu SJ, Yang L. The prognostic effect of statin use on urologic cancers: an updated meta-analysis of 35 observational studies. Medicine (Baltimore) 2015; 94: e1523.