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SYSTEMATIC REVIEW AND META-ANALYSIS

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The Prognostic Effect of Statin Use on Urologic Cancers

An Updated Meta-Analysis of 35 Observational Studies

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Abstract: Recent studies suggest that statin may benefit cancer prognosis, especially through its radiosensitization effect. But controversy exists in other studies. Hence, we performed a meta-analysis of results from 35 studies to evaluate the effect of statin use on urologic cancers.

We conducted computerized search from PubMed, Embase, and ISI Web of Knowledge through May 2015, screened the retrieved references, and collected and evaluated relevant information. We extracted and synthesized corresponding hazard ratios (HR) and confidence interval (CI) by using Review Manager 5.3 and STATA 13. This review was registered at PROSPERO with registration No. CRD42015020171.

We selected total 35 retrospective studies and conducted a meta-analysis of results from these studies. The pooled results suggested no benefit of statin use to bladder cancer and renal cell carcinoma, except overall survival [HR = 0.81, 95% CI: 0.69–0.96]. However, significant improvement of prostate cancer prognosis including overall survival [HR = 0.82, 95% CI: 0.70–0.97] and cancer-specific survival [HR = 0.70, 95% CI: 0.59–0.83] was indicated, but not including tumor progression [HR = 0.84, 95% CI: 0.62–1.14]. Statin use improved biochemical recurrence of prostate cancer in radiotherapy patients [HR = 0.68, 95% CI: 0.54–0.85] but not in radical prostatectomy patients [HR = 0.97, 95% CI: 0.82–1.15].

Current evidence suggests no benefit of statin use to bladder cancer and renal cell carcinoma, except in overall survival. While statin use benefited prostate cancer patients in overall survival, cancer-specific survival but not in tumor progression; it also improved biochemical recurrence in radiotherapy patients but not in radical patients. To verify these results, randomized controlled trials are necessary.

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Abbreviations: 95% CI = 95% confidence interval, BC = bladder cancer, BCG = bacille Calmette–Guérin, BCR = biochemical recurrence, CSS = cancer-specific survival, HR = hazard ratio, NOS = Newcastle–Ottawa Scale, OS = overall survival, PCa = prostate cancer, PFS = progression-free survival, RCC = renal cell carcinoma, RFS = recurrence-free survival.

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S-JF and LY conceived and designed this research. YL and D-LS performed the literature search, bias assessment of included studies, and data extraction. S Zhang and HX conducted data analysis. S Zhang, D-LS, HX, and YL coauthored the manuscript. LY and S-JF gave methodological guidance during the research and made the final revision of the manuscript.

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INTRODUCTION

Statin is a 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor and widely used for hypercholesterolemia patients. Recent studies prompt to indicate statin as a panacea because of its effects in treating variant diseases. A previous study showed that statin use was a protective factor for cancer incidence risk.[1] To date, statin is known as a pleiotropic drug rather than cholesterol-lowering medication. A retrospective survey of Shared Equal Access Regional Cancer Hospital (SEARCH) database indicated that triglycerides and low-density lipoproteins were associated with increased risk of prostate cancer recurrence. In the contrary, high-density lipoproteins were associated with decreased risk of prostate cancer in dyslipidemia.[2] It is compatible with the conclusion of another study that statin use significantly reduces breast cancer mortality.[3] Similar outcomes were also observed in numerous urological cancer treatment studies. However, controversy of real effect existed in variant studies.[4,5] Hence, we aimed to conduct a meta-analysis of well selected observational studies to evaluate prognostic effect of statin use in urinary cancer treatment, limited in renal cell carcinoma, bladder cancer, and prostate cancer. This study was registered in PROSPERO with registration number CRD42015020171.[6]

METHODS

Search and Screen Strategy

We performed a systematic literature search of PubMed, Embase, and ISI Web of Knowledge to retrieve urologic cancer clinical studies using statin through May 3, 2015. We used search key words including *statin*, *renal cell carcinoma*, *bladder cancer*, *prostate cancer*, *survival* and *mortality*, etc. The detailed search strategy was described in the *supplement* 1. The citations in the retrieved articles were also screened for any relevant studies. The initial screen was conducted by reviewing the title and abstract by 2 independent investigators (YL and DLS) to eliminate the irrelevant articles. Then, the full-text articles were reviewed according to eligibility criteria. Any clinical study comprising the evaluation of statin use on urologic cancer prognosis was eligible. In this article, we only include results of renal cell carcinoma (RCC), bladder cancer (BC), and prostate cancer (PCa). Articles that has abstract only, duplicated literature, overlapping patients or duplicated data presented in conferences; or does not study RCC, BC or PCa; or has no data available, were excluded. In this study, all data and analyses were based on the previous published studies, and thus no ethical approval and patient consent are required.

Data Extraction and Quality Assessment

Before data collection, a spreadsheet was designed for the key information. Data extraction was independently performed by 2 researchers (YL and DLS) and cross-checked. Meanwhile, any disagreement or uncertainty was resolved by group discussion. Data extracted from the articles included the name of the first author and publication year, country, cancer type, recruitment period, number of patients, age, main treatment, follow-up, prognostic outcomes, definition of outcomes, and adjusted factors. The data were extracted from the original articles. During data extraction, multivariate outcomes were prior to univariate outcomes when both were provided, while if no multivariate results were presented, univariate outcomes were used instead. If there was no exact time to event survival data, we either estimated HR and 95% CI by the methods that were provided by Tierney et al[7] using the given survival or mortality curve or other available data, or referred previous study outcomes[8] or contacted the corresponding author for the original data. The extracted data from studies which have potential overlapping patients were removed before meta-analysis to avoid over-analysis. The quality assessment was carried out by using Newcastle–Ottawa Scale (NOS) for cohort study that comprised 3 domains with 8 items to evaluate bias risk.[9] Above 5 stars of total 9 stars was deemed as good quality.

Statistical Analysis

Review Manager 5.3 (The Cochrane Collaboration, Copenhagen) was used to perform quantitative synthesis. Hazard ratio (HR) and its 95% confident interval were used to evaluate the survival outcome. First, Cochran's Q test and Higgins I^2 statistic were calculated for heterogeneity detection.[10] $P \geq 0.1$ and $I^2 \leq 50\%$ were deemed to no significant heterogeneity, and fixed effects model was used. Otherwise, random effects model was used. The inverse variance method was used to calculate the pooled hazard ratio. Sensitivity analysis was conducted by using the method of leave-one-out to test the feasibility of the pooled results. Publication bias was detected with Egger's regression intercept test and was only performed in outcomes comprised more than 10 studies by using STATA 13 (Stata Corp LP, College Station, TX).[10,11] A 2-tailed $P < 0.05$ was considered statistically significant.

RESULTS

Eligible Studies and Quality Assessment

In total, 526 abstracts were retrieved by the initial search strategy. After screening, 35 studies[4,5,12–44] including a France article[31] were included in the qualitative and quantitative synthesis. The screening diagram was shown in Figure 1. The characteristics of included studies and the Newcastle–Ottawa Scale (NOS) quality assessment were shown in Table 1. Outcomes included overall survival, cancer-specific survival, recurrence-free survival, progression-free survival, and biochemical recurrence.

Survival Outcomes

In renal cell carcinoma, 4 studies were included.[15–18] Among them, 3 reported overall survival, 2 reported cancer-specific survival, and 3 reported tumor progression status. As shown in Figure 2, the pooled results of statin use in overall survival, cancer-specific survival, and tumor progression of renal cell carcinoma were HR = 0.81 (95% CI: 0.69–0.96), 0.72 (0.35–1.50), and 0.91 (0.54–1.55), respectively.

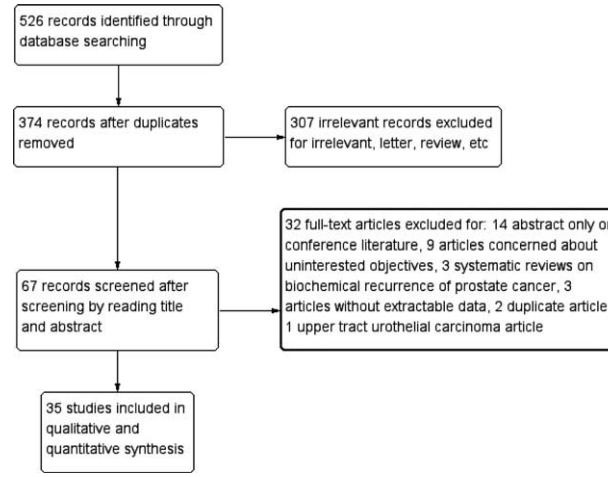

FIGURE 1. Literature screen diagram.

Three bladder cancer studies reported oncological prognosis.[12–14] One study reported overall survival with HR = 1.14 (0.89–1.44). Two studies reported cancer-specific survival and the pooled result was HR = 1.06 (0.87–1.29). Three studies reported recurrence-free survival with pooled HR = 1.05 (0.94–1.18). Two studies reported tumor progression and the pooled HR was 0.87 (0.65–1.15). All results were calculated by applying fixed effect model and shown in Figure 3.

Among prostate cancer studies, 5 reported overall survival outcomes and the pooled HR of statin use versus nonstatin use was 0.82 (0.70–0.97). Accordingly, 6 studies presented cancer-specific survival outcomes, the pooled result was HR = 0.70 (0.59–0.83). Tumor progression was reported in 5 studies and the pooled risk was 0.84 (0.62–1.14). All the above 3 clinical outcomes were analyzed by using the randomized effect model shown in Figure 4. Additionally, biochemical recurrence of prostate cancer became important in statin anticancer research. All prostate cancer studies subgroup were stratified by major treatment method and a subgroup analysis was conducted considering its radiosensitization effect. In radical prostatectomy subgroup, 13 studies presented biochemical result and the pooled hazard ratio of statin use versus nonstatin use was 0.97 (0.82–1.15), $P = 0.73$. However, in radiotherapy subgroup, 7 references reported biochemical recurrence, the pooled HR was 0.68 (0.54–0.85), $P = 0.0009$. Figure 5 shows the forest plot of biochemical recurrence of prostate cancer.

Publication Bias and Sensitivity Analysis

Publication bias detection was conducted by Egger's asymmetric test only in biochemical recurrence. P value of the linear regression was 0.803 for radical prostatectomy subgroup, 0.977 for radiotherapy subgroup, and 0.463 for the entire group of prostate cancer. The results show that no significant publication bias was observed and the funnel plot is shown in Figure 6. A sensitivity analysis was conducted in prostate cancer. There is no significant change observed in cancer-specific survival, tumor progression, and biochemical recurrence after removing any included study (results were omitted).

DISCUSSION

Among medical studies, there is a great controversy on the effect of statin. Antitumor and tumor promotion effect are both

TABLE 1. Characteristics of Included Studies

Study	Country	Cancer	Duration	N of pts (Statin/Non-statin)	Age (yr)	Treatment	Follow -up (month)	Outcomes	Definition of outcomes	Adjusted factors	NOS
Berglund 2008	USA	BC	1978.7–2006.11	245/707	Mn = 66 (R: 57–75)	BCG	NA	RFS, PFS	**Recurrence**: visual and/or biopsy proven at cystoscopy or positive repeat cytology **Progression**: progression to surgery	T stage, Grade	5
Crivelli 2013	Multinational	NMIBC	1996–2007	341/776	Md = 67 (IQR: 59–75)	TURB	Md = 62.7 (IQR: 25–110.7)	RFS, PFS, OS, CSS	**Recurrence**: first tumor relapse in bladder regardless of stage **Progression**: muscle-invasive relapse in bladder	Univariable COX regression	5
da Silva 2013	Multinational	MIBC	1992–2008	642/860	Md = 66 (IQR: 59–73)	RC	Md = 34 (IQR: 17–61)	RFS, CSS	**Recurrence**: tumor relapse in operative field, regional lymph node and/or metastasis	Age, Sex, BMI, Smoking, pT stage, Grade, STSM, LVI, Concomitant CIS, Lymph node, AC	7
Choi 2013	Korea	RCC	2006.1–2012.6	21/94	Mn = 64.1 ± 8.4	RN or PN	NA	PFS	**Progression**: recurrence and progression of RCC	Age, Sex, BMI	5
Hamilton 2014	USA	RCC	1995–2010	708/1900	Md: 66/59	RN or PN	Md = 36	PFS, OS	**Progression**: metastases or death from RCC	Age, Sex, Race, surgery type, Charlson comorbidity score, pT stage, Preop GFR, symptom, year of surgery	6
Kaffenberger 2015	USA	RCC	2000–2010	270/646	Md = 60.8 (IQR: 51.3–69.3)	RN or PN	Md = 42.5 (IQR: 19.1–67.1)	OS, CSS	—	Age, ASA, pT stage, Grade, lymph node, metastases, hypercalcemia, anemia, blood type	7
Viers 2015	USA	RCC	1995–2009	630/1727	Md = 63 (IQR: 54–71)	RN or PN	Md = 7.8yrs (IQR: 5.3–11.2) for alive pts	PFS, OS, CSS	**Progression**: distant metastases or death from RCC	Age, Sex, Race, symptoms, smoking, ECOG PS, Charlson comorbidity score, histology, BMI, tumor size, pT stage, Grade, coagulative tumor necrosis, Sarcomatoid differentiation	6
Caon 2014	Canada	PCa (localized)	2000.1–2007.12	914/2937	Mn = 70.3 (R: 45–88)	EBRT	Md = 8.4yrs	CSS	—	Age, aspirin, year of treatment, radiation dose, ADT, initial PSA, T stage, Charlson index, GS	7
Chao 2013-RP	USA	PCa	2004–2005	446/738	Mn = 60 ± 6.8	RP	Mn = 4.3 ± 1.3yrs	PFS, BCR	**Progression**: metastases or prostate cancer related death **BCR**: a single PSA>0.2ng/ml after undetectable PSA measurement after surgery	Age, Race, stage, GS, preop PSA, interval from diagnosis to surgery, obesity	7
Chao 2013-RT	USA	PCa	2004–2006	401/373	Mn = 68.4 ± 7.0	EBRT	Mn = 4.1 ± 1.4yrs	BCR	**BCR**: a rise in PSA by 2 ng/ml or greater above nadir PSA after RT (Phoenix nadir +2)	Race, stage, GS, pre-RT PSA, hypertension, neoadjuvant therapy, interval from diagnosis to RT	7
Cuaron 2015	USA	PCa (localized)	1998–2010	273/481	NA	BT	Md = 48 (R: 1–156)	BCR	**BCR**: Phoenix nadir +2 standard	Neoadjuvant hormone therapy, GS, additional EBRT	6
Geybels 2013	USA	PCa	2002.1–2005.12	289/712	Mn = 61.5 ± 7.8	RP or RT or ADT, etc	NA	PFS, CSS	**Progression**: CSS, metastatic cancer, received secondary treatment, rise in PSA	Age, GS, stage, PSA level, primary treatment, Race, family history, BMI, smoking, alcohol consumption, aspirin, non-aspirin NSAID use, DM, PCa screening history	8
Grytli 2014	Norway	PCa (high risk or metastases)	2004–2009	1004/2695	Mn = 76.3 ± 8.1	NA	Md = 39	CSS	—	Aspirin, Age, PSA, GS, clinical T stage, matastases, performance status, ADT initiated within 6 months after diagnosis	7
Gutt 2010	USA	PCa (nonmetastatic)	1988–2006	189/502	Md = 69 (R: 42–83)	EBRT or BT	Md = 50 (R: 0.4–276)	PFS, BCR	**Progression**: BCR, metastases, salvage ADT, OS	pT stage, GS, log PSA, RT dose, hormone therapy	7

Study	Country	Cancer	Duration	N of pts (Statin/Non-statin)	Age (yr)	Treatment	Follow -up (month)	Outcomes	Definition of outcomes	Adjusted factors	NOS
Hamilton 2010	USA	PCa	1988–2008	236/1083	Mn = 60.96 ± 6.48	RP	Md = 24/38 (R: 11–68)	BCR	**BCR**: Phoenix nadir +2 standard **BCR**: a single PSA>0.2 ng/ml, 2 concentrations at 0.2 ng/ml, or secondary treatment postop detectable PSA	Age, Race, medical center, biopsy GS, clinical stage, BMI, log PSA, percentage of positive cores, year of surgery, pathologic GS, extracapsular extension, seminal vesicle invasion, positive margin, lymph node	7
Ishak-Howard 2014	USA	PCa	1999–2009	258/281	Mn = 56.5 ± 7.6	RP	Mn = 94.9 ± 56.6	BCR	BCR: a single PSA >0.4 ng/ml after an undetectable PSA after surgery	Age, BMI, NSAID use, pathologic GS, prediagnostic PSA, clinical stage, year of surgery	7
Katz 2010	USA	PCa	1990–2003	1824/5218	Mn = 64.4 ± 7.8	RP or RT	Md = 4 (R: 0–16) yrs	OS	—	NSAIDs use, mean office visits, Age, cardiovascular disease, year of diagnosis, pT stage, DM, biopsy GS, smoking	6
Kollmeier 2011	USA	PCa (localized)	1995.1–2007.8	382/1299	NA	TDCRT or IMRT	Md = 5.9 (R: 0–14) yrs	OS, CSS, BCR	**BCR**: Phoenix nadir +2 standard	Age, T stage, GS, pretreatment PSA, NCCN risk group, ADT, RT dose	8
Kontraros 2013	Greece	PCa	1999.1–2010.4	107/481	Mn = 65.2 ± 5.7	RP	Md = 3.4 (IQR: 1.5–5.0) yrs	BCR	**BCR**: NA	Age, BMI, aspirin use, DM, log preop PSA, prostate volume, GS, inflammation, clinical T stage, pT stage, RT, positive margin	6
Ku 2011	Korea	PCa	1997.5–2009.4	87/600	Mn = 65.2 ± 6.7	RP	Md = 38 (R: 3–143)	BCR	**BCR**: a single PSA of 0.2 ng/ml or greater	Age, BMI, ASA, comorbidity, prostate volume, PSA, clinical stage, year of surgery, percentage of positive score, biopsy GS, percentage of tumor volume, pathologic GS, margin status, extracapsular extension, seminal vesicle invasion	6
Misrai 2012	France	PCa	2004–2008	97/280	Md = 64 (R: 48–76)	RP	Mn = 33 ± 10	BCR	**BCR**: consecutive twice PSA >0.2 ng/ml after surgery	D'Amico risk group, obesity, DM, marginal positive	6
Moyad 2006	USA	PCa (localized)	1995.4–2002.6	191/747	Mn = 66.1 ± 7.2	BT	Mn = 5.6 ± 2.1 yrs	OS, CSS, BCR	**BCR**: PSA>0.4 ng/ml after nadir	Age, pretreatment PSA, percentage of positive biopsy, prostate volume, GS, EBRT, Isotope, tobacco, hypertension, DM, perineural invasion, ADT, risk group, stage	7
Oh 2015	USA	PCa	1999.1–2009.2	174/73	Md = 62 (R: 45.6–81.9)	BT	Md = 51 (R: 9.4–140.35)	BCR	**BCR**: Phoenix nadir +2 ng/ml after RT	T stage, GS, PSA, radiation dose	7
Rieken 2013	Multinational	PCa (localized)	2000–2011	2275/4567	Mn = 61.3 ± 6.7	RP	Md = 25 (IQR: 8–42)	BCR	**BCR**: PSA > 0.2 ng/ml on two consecutive visits	Age, preop PSA, RP GS, lymph node, surgical margin, pT stage	6
Ritch 2011	USA	PCa	1990–2008	281/980	Md = 60	RP	Md = 36	BCR	**BCR**: PSA> 0.2 ng/ml after a previously undetectable PSA 3 months postoperatively	Age, Race, log PSA, pT stage, pathologic GS, margin status, year of surgery	6
Song 2015	Korea	PCa	1998–2011	452/1685	Md = 67 (IQR: 63–71) for non-statin users	RP	Md = 39.4 (R: 8–183)	BCR	BCR: PSA >0.2ng/ml	Age, DM, PSA, pathologic GS, pT stage, surgical margin	7
Soto 2009	USA	PCa (localized)	1987.1–2006.7	220/748	Mn = 68.2 ± 7.3	TDCRT or IMRT	Md = 3.2 (R: 0.2–16.5) yrs	PFS	**Progression**: BCR (Phoenix PSA nadir +2 ng/ml or salvage ADT) or clinical failure or death	Age, T stage, pre-RT PSA, GS, RT dose, pelvic RT, ADT, year of treatment	6

Study	Country	Cancer	Duration	N of pts (Statin/Non-statin)	Age (yr)	Treatment	Follow -up (month)	Outcomes	Definition of outcomes	Adjusted factors	NOS
Yu 2014	UK	PCa (nonmetastatic)	1998.4–2009.12	3407/8365	Mn = 71.3 ± 8.8	RP or RT or ADT or Chemotherapy	Mn = 4.4 ± 2.9 yrs	OS, CSS	—	Age, year of diagnosis, Race, alcohol use, smoking, obesity, chronic kidney disease, myocardial infarction, ischemic stroke, transient ischemic attack, peripheral artery disease, previous cancers, PSA level, GS, metformin, sulfonylureas, thiazolidinediones, insulins, other oral antihypoglycemic agents, ACEI, ARB, CCB, β-blockers, diuretics, other antihypertensive drugs, aspirin, other NSAIDs, 5α-reductase inhibitors, prediagnostic statin use, PSA testing activity, prostatectomy, RT, chemotherapy, ADT	7
Zaorsky 2012	USA	PCa (nonmetastatic)	1989–2006	691/1360	Md = 69 (R: 36–86)	TDCRT or IMRT	Md = 75 (R: 18–239)	BCR	**BCR**: PSA nadir +2 ng/ml	NA	6
Choe 2012	USA	PCa (localized)	Since 1995	Total 5955	Md = 64 (R: 39–86)	RP or RT	Md = 70 (R: 1–352)	CSS	—	Aspirin, non-aspirin coagulant, log PSA, GS, clinical T stage, treatment type	7
Mass 2012	USA	PCa (localized)	2000.10–2008.6	437/1009	Mn = 58.4 ± 6.9	RP	Md = 57	BCR	**BCR**: PSA greater than 0.2 ng/ml with a confirmatory reading above this threshold	Age, preop PSA, pT stage, pathologic GS, Race	6
Krane 2010	USA	PCa	2001.1–2008.8	1031/2797	Mn = 59.9 ± 7.3	RP	Mn = 26	BCR	**BCR**: a single PSA of 0.2 ng/ml or greater with another increasing value	Log PSA, pathologic grade, pT stage, surgical margin	6
Mondul 2011	USA	PCa (localized)	1993.1–2006.3	386/2012	Mn = 56.3	RP	Md = 7 yrs	PFS, BCR	**Progression**: metastases or death **BCR**: NA	Age, Race, PCa family history, aspirin use, ACEI, BMI, pT stage, pathologic GS, preop PSA, year of surgery	8
Niraula 2013	Multinational (TAX 327)	mCRPC	2000.3–2002.6	82/924	Md = 68 (R: 36–92)	Docetaxel	NA	OS	—	Treatment group, baseline pain, baseline Karnofsky performance status	5
Cattarino 2015	France	PCa (localized)	2009–2014	156/435	Md = 62.8 (IQR: 49.1–69.2)	RP	Md = 42.3 (IQR: 25.8–59.9)	BCR	**BCR**: two consecutive PSA> 0.2ng/ml with 3 month delay	—	5

AC = adjuvant chemotherapy; ACEI = angiotensin-converting enzyme inhibitors; ADT = androgen deprivation therapy; ARB = angiotensin receptor blockers; ASA = American Society of Anesthesiology physical status; BC = bladder cancer; BCG = bacille Calmette– Guérin; BCR = biochemical recurrence; BMI = body mass index; BT = brachytherapy; CCB = calcium channel blockers; CSS = cancer-specific survival; DM = diabetes mellitus; EBRT = external beam radiation therapy; ECOG PS = The Eastern Cooperative Oncology Group Performance Status; GS = Gleason score; IMRT = intensity-modulated radiotherapy; IQR = interquartile range; LVI = lymphovascular invasion; mCRPC = metastatic castration refractory prostate cancer; Md = midian; MIBC = muscle invasive bladder cancer; Mn = mean; N of pts = number of patients; NA = not applicable; NMIBC = non-muscle invasive bladder cancer; NOS = Newcastle–Ottawa Scale; NSAID = nonsteroidal anti-inflammatory drug; OS = overall survival; PCa = prostate cancer; PFS = progression-free survival; PN = partial nephrectomy; R = range; RC = radical cystectomy; RCC = renal cell carcinoma; RFS = recurrence-free survival; RN = radical nephrectomy; RP = radical prostatectomy; RT = radiation therapy; TDCRT = three-dimensional conformal radiotherapy; TURB = transurethral resection of bladder; yrs = years.

N of pts could not be exactly equal to patients who analyzed in survival analysis. OS and CSS were recognized definition. Any n/m meant statin user content/non-statin user content. Any n ± m meant mean±standard deviation.

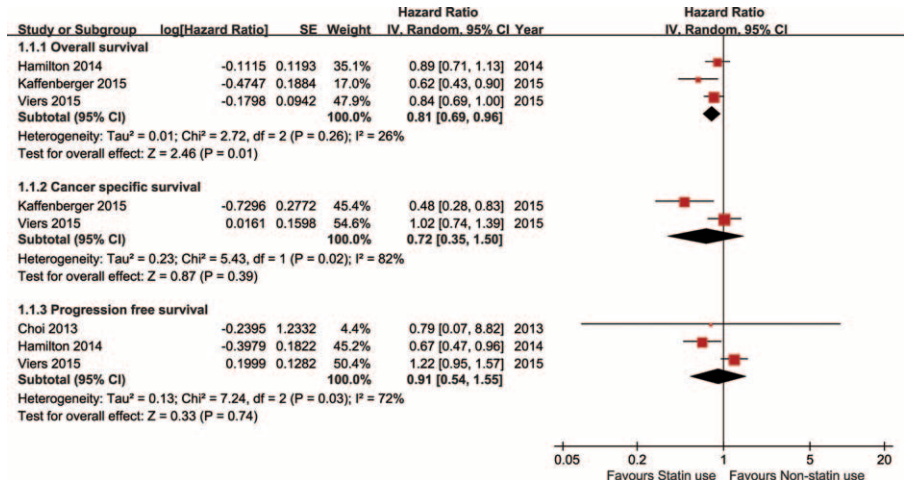

FIGURE 2. Statin use on survival outcomes of renal cell carcinoma (RCC).

presented in variant studies.[45,46] However, the mechanism of antitumor or tumor promotion effect of statin has not yet been clearly elucidated. Hindler et al[47] summarized the role of statin in cancer therapy as 4 aspects: First, statin inhibits tumor cell growth by inhibiting dolichol, geranylpyrophosphate, and farnesylpyrophosphate that are regulators of cell cycle, by inhibiting Ras and Rho that mediate cell proliferation, and by stabilizing the cell cycle kinase inhibitors p21 and p27. Second, inhibition of angiogenesis: statin has pros and cons for angiogenesis. High dose statin has an antiangiogenesis effect by inhibiting capillary tube formation and reducing vascular endothelial growth factor release. However, low-dose statin has a proangiogenesis effect by stimulating protein kinase B and activating endothelial nitric oxide synthase. Third, statin induces cell apoptosis by upregulating proapoptotic proteins and reducing antiapoptotic proteins. Fourth, statin suppresses tumor metastasis by reducing the expression of endothelial leukocyte adhesion molecule E-selectin and matrix metalloproteinase, inhibiting epithelial growth factor induced tumor cell invasion. Sun et al[48] demonstrated that cholesterol increases Ca^{2+} entry via the TRPM7 channel, which promotes proliferation of prostate cells by inducing the activation of the AKT and/or the ERK pathway. Additionally, cholesterol-mediated Ca^{2+} entry induces an increase of calpain activity that represses E-cadherin expression, which could lead to migration of prostate cancer cells. Ban?ez et al[49] reported that statin use significantly reduced the risk of inflammatory infiltration in prostate cancer, which was proved to be associated with cancer development and prognosis.[50–53] All the above studies attend to elucidate the possible anti-cancer mechanism of statin. While in clinical studies, there is also a great controversy on the effect of statin use for cancer patients' prognosis. Hoffmann et al[54] reported that non-muscle-invasive bladder cancer patients, who were treated with bacille CalmetteGuéérin (BCG)

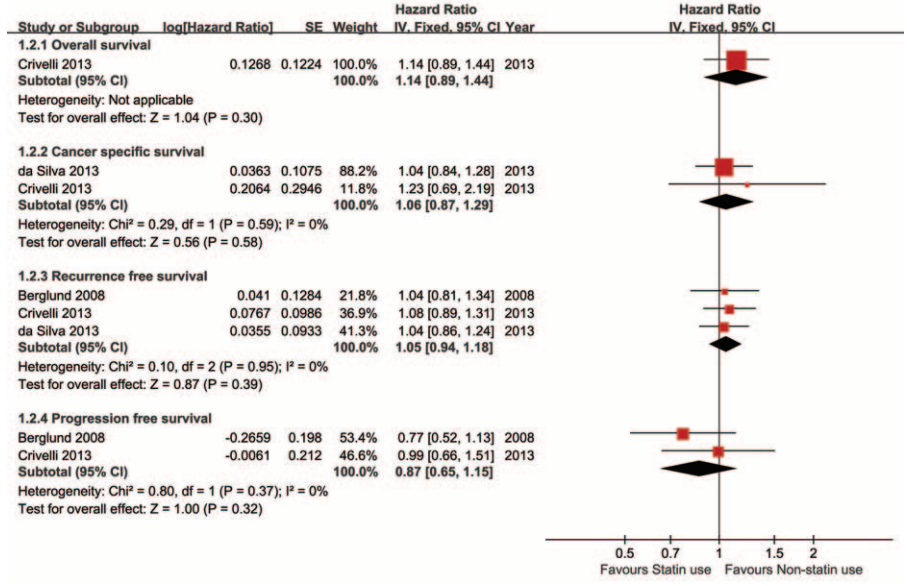

FIGURE 3. Statin use on survival outcomes of bladder cancer (BC).

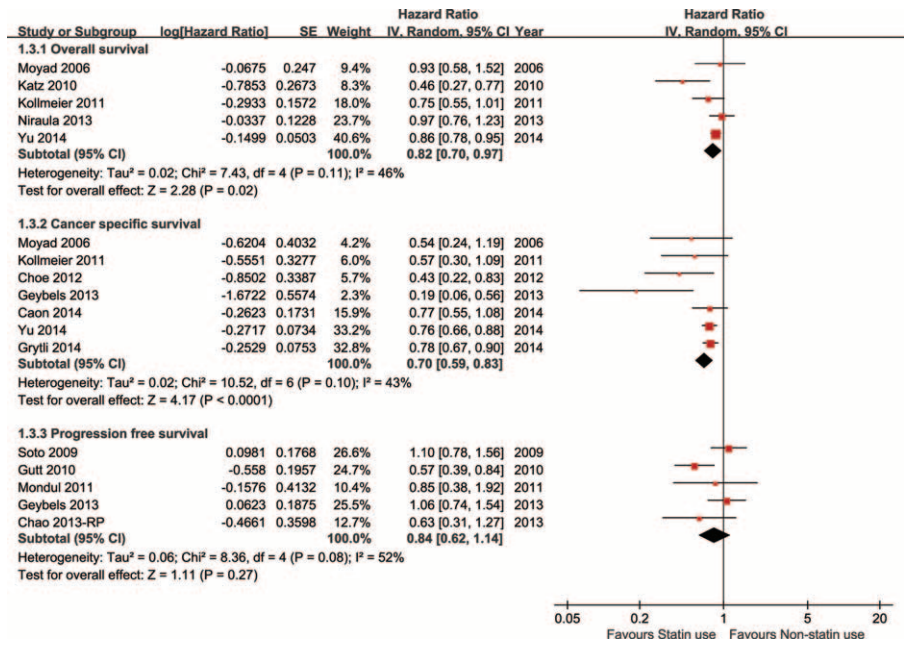

FIGURE 4. Statin use on survival outcomes of prostate cancer (PCa).

immunotherapy and were exposed to statin use, had worsening prognosis. This study was subsequently questioned by Kamat et al.[55] They reported no significant difference in the tumor recurrence, progression, or deaths in their cohort with 156 patients treated with BCG. A large cross-sectional study reported that statin use was associated with a reduction in the probability that older men would have an abnormal screening PSA result regardless of the PSA threshold ($PSA > 2.5, > 4.0,$ or > 6.5 ng/mL). This reduction is more pronounced with higher statin dose, longer statin duration, and higher statin potency.[56] It revealed the anti-cancer effect of statin. Additionally, statin has a radiosensitization effect for prostate cancer both in vitro and in vivo.[25,28,57] However, some studies do not support this synergism.[21,22] Our analysis shows significant effect of statin use in prostate cancer patients underwent radiotherapy but not in patients with radical prostatectomy.

In our study, we investigated 4 clinical outcomes and 1 biochemical outcome in 3 major urologic cancers. In renal cell carcinoma treatment, statin use was associated with improvement of overall survival but not in cancer-specific survival and tumor progression. The improvement of overall survival in

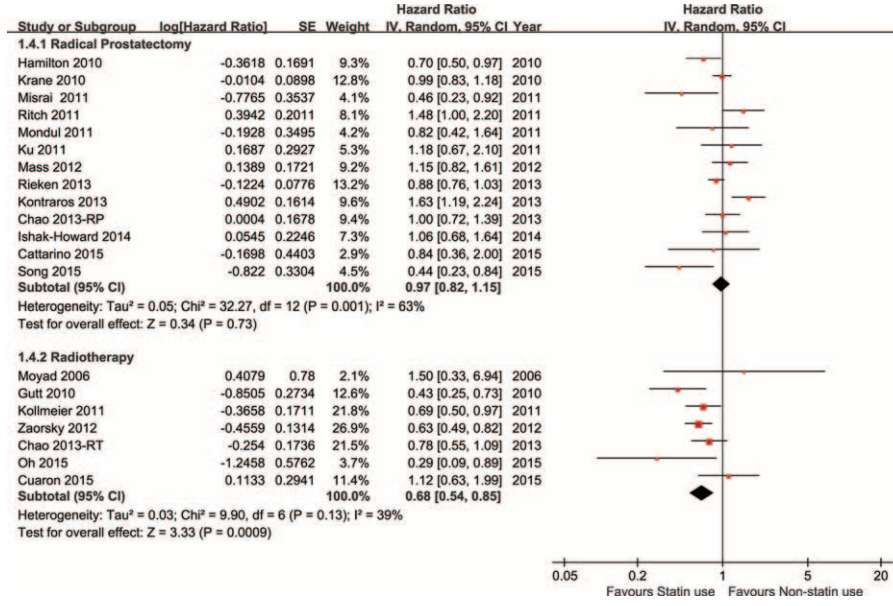

FIGURE 5. Stain use on biochemical recurrence (BCR) of prostate cancer (PCa).

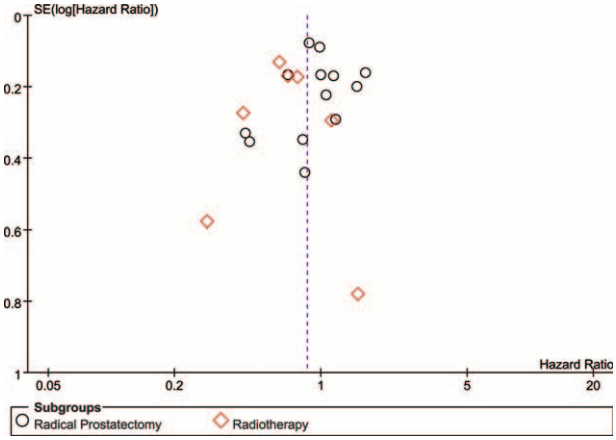

FIGURE 6. Funnel plot of included studies concerning biochemical recurrence (BCR).

statin use patients was not stable and probably was derived from the protection from cardiovascular-related death.[58] In bladder cancer, no significance improvement was observed in overall survival, cancer-specific survival, or tumor recurrence and progression. A possible explanation for these results is that the inherent poor prognosis of bladder cancer overcomes the anticancer effect of statin use, or because of its intracavity. The biological behavior of bladder cancer could also be a risk for drug effect because even though in chemotherapy, numerous drug resistant or insensitive bladder cancer existed.[59] In prostate cancer, significant improvements of overall survival and cancer-specific survival, not tumor progression, were observed. Meanwhile, biochemical recurrence of PSA was intensively analyzed. Referred to previous study,[8] stratification by major treatment methods was performed. In radical prostatectomy subgroup, no difference was observed between statin use and non-use. However, statin use significantly improved biochemical recurrence in prostate cancer patients treated with radiotherapy. Sensitivity analysis described as above did not alter the results. It is compatible with the radiosensitization effect of statin use. There seemed to be a paradox that statin use did not improve biochemical recurrence in radical prostatectomy patients but improve overall survival and cancer-specific survival. A hypothesis was that these benefits derived from radiation therapy patients. But it has not been verified. Additionally, as to clinical outcomes, small study effect was an obvious risk for the pooled results. Generally, statin use seemed to benefit prostate cancer, especially prostate cancer patients underwent radiotherapy.

Additionally, all studies included or excluded were obviously biased. Statin, unlike chemotherapeutic drugs, is a gentle medication for cancer, if it has the anticancer effect. However, the accumulative effect of statin use is unclear yet. On the other hand, the definition of statin use has not been clearly elaborated. The statin category is also different from each type. Additionally, statin use was a time-dependent covariate in these survival cohorts. Stratifying statin users by records of pre or at cancer diagnosis or treatment is not appropriate. First, the duration of statin use is volatile. A man consumed statin for 5 years is different from the man with 5-month statin consumption. Second, the statin use status of included patients was also volatile during the follow-up. For example, a statin use patient could discontinue statin consumption. Mostly, those nonstatin users could consume statin after diagnosis or treatment of cancer. This would obviously confound the survival analysis. Based on thus, randomized controlled trials would help verify this benefit. Additionally, it is too early to apply statin medication to urologic cancer patients. Adverse effect, dose, and economic factors were important obstacles that must be overcome before application though significant benefit was verified by randomized controlled trials in the future.

CONCLUSION

Our meta-analysis summarized the published literature with statin use exposure and the pooled results suggested no benefit of statin use to bladder cancer and renal cell carcinoma, except in overall survival. However, significant improvement of prostate cancer prognosis including overall survival and cancer-specific survival was indicated, but not including tumor progression. Statin use improved biochemical recurrence of prostate cancer in radiotherapy patients but not in radical prostatectomy patients. Randomized controlled trials would help verify these results.

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