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.

**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 using the given survival or mortality curve or other available data, or referred previous study outcomes 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. 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% confidence interval were used to evaluate the survival outcome. First, Cochran’s Q test and Higgins I² statistic were calculated for heterogeneity detection. P ≥ 0.1 and I² ≤ 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 studies4,5,12–44 including a France article43 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 included15–18 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.

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 HR = 0.73 (0.70–0.79). 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>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Cancer</th>
<th>Duration</th>
<th>N of pts (Statin/Non-statin)</th>
<th>Age (yr)</th>
<th>Treatment</th>
<th>Follow-up (month)</th>
<th>Outcomes</th>
<th>Definition of outcomes</th>
<th>Adjusted factors</th>
<th>NOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berglund 2008</td>
<td>USA</td>
<td>BC</td>
<td>1978.7–2006.11</td>
<td>245/707</td>
<td>Mn=66/70</td>
<td>BCG</td>
<td>NA</td>
<td>RFS, PFS</td>
<td>Recurrence: visual/or biopsy proven at cystoscopy or positive repeat cytology</td>
<td>T stage, Grade</td>
<td>5</td>
</tr>
<tr>
<td>da Silva 2013</td>
<td>Multinational</td>
<td>MBBC</td>
<td>1992–2008</td>
<td>642/800</td>
<td>Mn=61/70</td>
<td>RC</td>
<td>Md=34 (IQR: 17–61)</td>
<td>RFS, CSS</td>
<td>Recurrence: tumor relapse in operative field, regional lymph node and/or metastasis</td>
<td>Age, Sex, BMI, Smoking, pT stage, Grade, STS, LVI, Concomitant CIB, Lymph node, AC</td>
<td>7</td>
</tr>
<tr>
<td>Choe 2013</td>
<td>Korea</td>
<td>RCC</td>
<td>2006.1–2012.6</td>
<td>21/94</td>
<td>Mn=61/70</td>
<td>RN or PN</td>
<td>NA</td>
<td>PFS</td>
<td>Progression: recurrence and progression of RCC</td>
<td>Age, Sex, BSE, Smoking, pT stage, Grade, lymph node, metastasis, hypercalcaemia, anemia, blood type</td>
<td>6</td>
</tr>
<tr>
<td>Hamilton 2014</td>
<td>USA</td>
<td>RCC</td>
<td>1995–2010</td>
<td>70/1900</td>
<td>Md=66/59</td>
<td>RN or PN</td>
<td>Md=36</td>
<td>PFS, OS</td>
<td>Progression: metastases or death from RCC</td>
<td>Age, Sex, Race, symptoms, smoking, ECOG PS, Charlson comorbidity score, pT stage, Grade, coagulative tumor necrosis, Sarcomatoid differentiation</td>
<td>7</td>
</tr>
<tr>
<td>Kaifeng 2015</td>
<td>USA</td>
<td>RCC</td>
<td>2000–2010</td>
<td>270/646</td>
<td>Mn=60/80</td>
<td>RN or PN</td>
<td>Md=42.5 (IQR: 25–110.7)</td>
<td>OS, CSS</td>
<td>—</td>
<td>Age, ASA, pT stage, Grade, lymph node, metastasis, coagulative tumor necrosis, Sarcomatoid differentiation</td>
<td>7</td>
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<tr>
<td>Vier 2015</td>
<td>USA</td>
<td>RCC</td>
<td>1995–2009</td>
<td>630/1727</td>
<td>Mn=63/71</td>
<td>RN or PN</td>
<td>Md=7.8yrs (IQR: 5.3–11.2) for alive pts</td>
<td>PFS, OS, CSS</td>
<td>Progression: distant metastases or death from RCC</td>
<td>Age, Sex, Race, symptoms, smoking, ECOG PS, Charlson comorbidity score, pT stage, Grade, metastatic cancer, received secondary treatment, rise in PSA</td>
<td>6</td>
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<tr>
<td>Cair 2014</td>
<td>Canada</td>
<td>PCa (localized)</td>
<td>2000.1–2007.12</td>
<td>914/2937</td>
<td>Mn=70/3 (IQR: 45–88)</td>
<td>EBRT</td>
<td>Md=8.4yrs</td>
<td>CSS</td>
<td>—</td>
<td>Age, Race, stage, PSA, interval from diagnosis to surgery, obesity</td>
<td>7</td>
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<tr>
<td>Chao 2013-RP</td>
<td>USA</td>
<td>PCa</td>
<td>2004–2005</td>
<td>446/738</td>
<td>Mn=60/68</td>
<td>RP</td>
<td>Mn=4.3±1.3yrs</td>
<td>PFS, BCR</td>
<td>Progression: metastases or prostate cancer related death</td>
<td>Age, Race, stage, PSA level, primary treatment, Race, family history, BMI, smoking, alcohol consumption, aspirin, non-aspirin NSAID use, DM, PCa screening history</td>
<td>7</td>
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<tr>
<td>Chao 2013-RT</td>
<td>USA</td>
<td>PCa</td>
<td>2004–2006</td>
<td>437/133</td>
<td>Mn=68/40</td>
<td>EBRT</td>
<td>Mn=4.1±1.4yrs</td>
<td>BCR</td>
<td>BCR: a single PSA &gt;0.2ng/ml after undetectable PSA measurement after surgery</td>
<td>Race, stage, GS, pre-RT PSA, hyperproliferative, neoadjuvant hormone therapy, interval from diagnosis to RT</td>
<td>7</td>
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<tr>
<td>Cizoton 2015</td>
<td>USA</td>
<td>PCa (localized)</td>
<td>1998–2010</td>
<td>273/481</td>
<td>NA</td>
<td>BT</td>
<td>Md=48 (IQR: 1–156)</td>
<td>BCR</td>
<td>BCR: Phoenix nadir &gt;2 standard</td>
<td>Age, OS, GS, PSA, clinical T stage, metastasis, performance status, ADT initiated within 6 months after diagnosis</td>
<td>7</td>
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<tr>
<td>Gerybols 2013</td>
<td>USA</td>
<td>PCa</td>
<td>2002–2005.12</td>
<td>289/712</td>
<td>Mn=61.5±7.8</td>
<td>RP or RT or ADT, etc</td>
<td>NA</td>
<td>PFS, CSS</td>
<td>Progression: CSS, metastatic cancer, received secondary treatment, rise in PSA</td>
<td>Age, OS, PSA level, primary treatment, Race, family history, BMI, smoking, alcohol consumption, aspirin, non-aspirin NSAID use, DM, PCa screening history</td>
<td>8</td>
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<td>Grytli 2014</td>
<td>Norway</td>
<td>PCa</td>
<td>2004–2009</td>
<td>1004/2095</td>
<td>Mn=76.3±8.1</td>
<td>NA</td>
<td>Md=39</td>
<td>CSS</td>
<td>—</td>
<td>Aspirin, Age, PSA, GS, clinical T stage, metastasis, performance status, ADT initiated within 6 months after diagnosis</td>
<td>7</td>
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<tr>
<td>Gott 2010</td>
<td>USA</td>
<td>PCa (nonmetastatic)</td>
<td>1988–2006</td>
<td>149/502</td>
<td>Mn=69/83 (IQR: 42–83)</td>
<td>EBRT or BT</td>
<td>Md=50 (IQR: 64–276)</td>
<td>PFS, BCR</td>
<td>Progression: BCR, metastases, w/ or w/o ADT, OS</td>
<td>pT stage, GS, log PSA, RT dose, hormone therapy</td>
<td>7</td>
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<tr>
<td>Study</td>
<td>Country</td>
<td>Cancer</td>
<td>Duration</td>
<td>N of pts (Statin/Non-statin)</td>
<td>Age (yr)</td>
<td>Treatment</td>
<td>Follow-up (month)</td>
<td>Outcomes</td>
<td>Definition of outcomes</td>
<td>Adjusted factors</td>
<td>NOS</td>
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<td>Hamilton 2010</td>
<td>USA</td>
<td>PCa</td>
<td>1988–2008</td>
<td>236/1083</td>
<td>Mn =60.96 ± 6.48</td>
<td>RP</td>
<td>Md =24/38 (R: 11–68)</td>
<td>BCR</td>
<td></td>
<td>Age, Race, medical center, biopsy GS, clinical stage, BMI, log PSA, percentage of positive cones, year of surgery, pathologic GS, extracapsular extension, seminal vesicle invasion, positive margin, lymph node metastasis</td>
<td>7</td>
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<tr>
<td>Ishak-Howard 2014</td>
<td>USA</td>
<td>PCa</td>
<td>1999–2009</td>
<td>258/241</td>
<td>Mn = 56.5 ± 7.6</td>
<td>RP</td>
<td>Mn = 949 ± 56.6</td>
<td>BCR</td>
<td>a single PSA ≥0.2 ng/ml after an undetectable PSA, after surgery</td>
<td>Age, BMI, NSAID use, pathologic GS, pre-diagnostic PSA, clinical stage, year of surgery</td>
<td>7</td>
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<tr>
<td>Katz 2010</td>
<td>USA</td>
<td>PCa</td>
<td>1990–2003</td>
<td>182/45218</td>
<td>Mn = 64.4 ± 7.8</td>
<td>RP or RT</td>
<td>Md = 4.8 ± 0.16 yrs</td>
<td>OS</td>
<td></td>
<td>Age, BMI, NSAID use, mean office visits, Age, cardiovascular disease, year of diagnosis, T stage, DM, biopsy GS, smoking history</td>
<td>6</td>
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<tr>
<td>Kollmeier 2011</td>
<td>USA</td>
<td>PCa (localized)</td>
<td>1995.1–2007.8</td>
<td>382/1299</td>
<td>NA</td>
<td>TDCRT or IMRT</td>
<td>Md = 5.9 (R: 0–14) yrs</td>
<td>OS, CSS, BCR</td>
<td>BCR: Phoenix nadir + 2 standard</td>
<td>NSAIDs use, mean office visits, Age, cardiovascular disease, year of diagnosis, T stage, DM, biopsy GS, smoking history</td>
<td>8</td>
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<tr>
<td>Kostros 2013</td>
<td>Greece</td>
<td>PCa</td>
<td>1999.1–2010.4</td>
<td>107/481</td>
<td>Mn = 65.2 ± 5.7</td>
<td>RP</td>
<td>Md = 3.4 (IQR: 1–5) yrs</td>
<td>BCR</td>
<td></td>
<td>Age, T stage, GS, pretreatment PSA, NCCN risk group, ADT, RT dose</td>
<td>6</td>
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<tr>
<td>Ku 2011</td>
<td>Korea</td>
<td>PCa</td>
<td>1997.5–2009.4</td>
<td>876/00</td>
<td>Mn = 65.2 ± 6.7</td>
<td>RP</td>
<td>Md = 38 (R: 3–143)</td>
<td>BCR</td>
<td>a single PSA ≥0.2 ng/ml or greater</td>
<td>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</td>
<td>6</td>
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<tr>
<td>Moreau 2012</td>
<td>France</td>
<td>PCa</td>
<td>2004–2008</td>
<td>972/80</td>
<td>Md = 64 (R: 46–76)</td>
<td>RP</td>
<td>Mn = 33 ± 10</td>
<td>BCR</td>
<td>consecutive twice PSA ≥0.2 ng/ml after surgery</td>
<td>D’Amico risk group, obesity, DM, marginal positive margin</td>
<td>6</td>
</tr>
<tr>
<td>Meyad 2006</td>
<td>USA</td>
<td>PCa (localized)</td>
<td>1995.4–2002.6</td>
<td>181/747</td>
<td>Mn = 66.1 ± 7.2</td>
<td>BT</td>
<td>Mn = 56 ± 21 yrs</td>
<td>OS, CSS, BCR</td>
<td>BCR: Phoenix nadir + 2 standard</td>
<td>Age, pretreatment PSA, percentage of positive biopsy, prostate volume, GS, EBR, dose, dosage, DM, lymph node, surgical margin, pT stage, positive margin</td>
<td>7</td>
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<tr>
<td>Oh 2015</td>
<td>USA</td>
<td>PCa</td>
<td>1999.1–2009.2</td>
<td>174/73</td>
<td>Md = 62 (R: 45.6–81.9)</td>
<td>BT</td>
<td>Md = 51 (R: 44–62)</td>
<td>BCR</td>
<td>PSA ≥0.4 ng/ml after nadir</td>
<td>Age, proop PSA, RP GS, lymph node, surgical margin, pT stage</td>
<td>7</td>
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<tr>
<td>Rieken 2013</td>
<td>Multinational</td>
<td>PCa (localized)</td>
<td>2000–2011</td>
<td>227/4567</td>
<td>Mn = 613 ± 6.7</td>
<td>RP</td>
<td>Md = 21 (R: 11–51)</td>
<td>BCR</td>
<td>BC: a single PSA &gt;0.2 ng/ml on two consecutive visits</td>
<td>Age, BMI, ASA, comorbidity, prostate volume, GS, EBR, dose, dosage, DM, lymph node, surgical margin, pT stage, positive margin</td>
<td>6</td>
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<tr>
<td>Ritch 2011</td>
<td>USA</td>
<td>PCa</td>
<td>1990–2008</td>
<td>281/980</td>
<td>Md = 60</td>
<td>RP</td>
<td>Md = 36</td>
<td>BCR</td>
<td></td>
<td>Age, Race, log PSA, T stage, pathologic GS, margin status, year of surgery</td>
<td>6</td>
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<tr>
<td>Soto 2009</td>
<td>USA</td>
<td>PCa (localized)</td>
<td>1987.1–2006.7</td>
<td>220/748</td>
<td>Mn = 68.2 ± 7.3</td>
<td>TEDCRT or IMRT</td>
<td>Md = 3.2 (R: 0.2–16.5) yrs</td>
<td>PFS</td>
<td>Progression: BCR (Phoenix PSA nadir + 2 ng/ml or salvage ADT) or clinical failure or death</td>
<td>Age, T stage, pro-RT PSA GS, RT dose, pelvic RT, ADT, year of treatment</td>
<td>6</td>
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<tr>
<td>Study</td>
<td>Country</td>
<td>Cancer</td>
<td>Duration</td>
<td>N of pts (Statin/Non-statin)</td>
<td>Age (yr)</td>
<td>Treatment</td>
<td>Follow-up (month)</td>
<td>Outcomes</td>
<td>Definition of outcomes</td>
<td>Adjusted factors</td>
<td>NOS</td>
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<td>Yu 2014</td>
<td>UK</td>
<td>PCa (nonmetastatic)</td>
<td>1998.4–2009.12</td>
<td>3407/8365 Mn/¼71.3/C68.8</td>
<td>RP or RT or ADT or Chemotherapy</td>
<td>Mn = 4.4 ± 2.9 yrs</td>
<td>OS, CSS</td>
<td>—</td>
<td>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, insulin, other oral antihyperglycemic agents, ACEI, ARB, CCB, beta-blockers, diuretics, other antihypertensive drugs, aspirin, other NSAIDs, 5α-reductase inhibitors, prediagnostic statin use</td>
<td>7</td>
<td></td>
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<tr>
<td>Zarosly 2012</td>
<td>USA</td>
<td>PCa (nonmetastatic)</td>
<td>Since 1995</td>
<td>691/1360 Md/¼69 (R: 36–86)</td>
<td>TDCRT or IMRT Md/¼75 (R: 18–239)</td>
<td>BCR</td>
<td>BCR: PSA nadir &gt; 2 ng/ml</td>
<td>NA</td>
<td>Aspirin, non-aspirin coagulant, logs PSA, OS, clinical T stage, treatment type</td>
<td>6</td>
<td></td>
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<tr>
<td>Mass 2012</td>
<td>USA</td>
<td>PCa (localized)</td>
<td>2000.10–2008.6</td>
<td>437/1009 Md/¼58.4/C66.9</td>
<td>RP</td>
<td>Md = 57</td>
<td>BCR</td>
<td>BCR: PSA greater than 0.2 ng/ml with a confirmatory reading above this threshold</td>
<td>Age, pT stage, pathologic GS, Race</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Kocz 2010</td>
<td>USA</td>
<td>PCa</td>
<td>2001.1–2008.8</td>
<td>1031/297 Md/¼59.9/C67.3</td>
<td>RP</td>
<td>Md = 26</td>
<td>BCR</td>
<td>BCR: a single PSA of 0.2 ng/ml or greater with another increasing value above this threshold</td>
<td>Log PSA, pathologic grade, pT stage, surgical margin</td>
<td>6</td>
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<tr>
<td>Mondal 2011</td>
<td>USA</td>
<td>PCa (localized)</td>
<td>1993.1–2006.3</td>
<td>386/2012 Md/¼56.3</td>
<td>RP</td>
<td>Md = 7 yrs</td>
<td>PFS, BCR</td>
<td>BCR: Progression metastases or death</td>
<td>Age, Race, PCa family history, aspirin use, ACEI, BMI, pT stage, pathologic GS, proph PSA, year of surgery</td>
<td>8</td>
<td></td>
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<tr>
<td>Niraula 2013</td>
<td>Multinational (TAX 327)</td>
<td>mCRPC</td>
<td>2000.3–2002.6</td>
<td>82924 Md/¼68 (R: 36–92)</td>
<td>Docetaxel</td>
<td>NA</td>
<td>OS</td>
<td>BCR</td>
<td>Treatment group, baseline pain, baseline Karnofsky performance status</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Cattarino 2015</td>
<td>France</td>
<td>PCa (localized)</td>
<td>2009–2014</td>
<td>156/435 Md/¼62.8 (IQR: 49.1–69.2)</td>
<td>RP</td>
<td>Md = 42.3 (IQR: 25.8–59)</td>
<td>BCR</td>
<td>BCR: two consecutive PSA &gt; 0.2 ng/ml with 3 month delay</td>
<td>—</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

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 = median; 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.
presented in variant studies. However, the mechanism of antitumor or tumor promotion effect of statin has not yet been clearly elucidated. Hindler et al 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 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. Banez et al 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. 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 reported that non-muscle-invasive bladder cancer patients, who were treated with bacille Calmette-Guérin (BCG)

![FIGURE 2. Statin use on survival outcomes of renal cell carcinoma (RCC).](image)

![FIGURE 3. Statin use on survival outcomes of bladder cancer (BC).](image)
immunotherapy and were exposed to statin use, had worsening prognosis. This study was subsequently questioned by Kamat et al.\textsuperscript{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.\textsuperscript{56} It revealed the anti-cancer effect of statin. Additionally, statin has a radiosensitization effect for prostate cancer both in vitro and in vivo.\textsuperscript{22,28,57} However, some studies do not support this synergism.\textsuperscript{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

\begin{figure}
\centering
\includegraphics[width=\textwidth]{statin_survival}
\caption{Statin use on survival outcomes of prostate cancer (PCa).}
\end{figure}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{statin_bcr}
\caption{Statin use on biochemical recurrence (BCR) of prostate cancer (PCa).}
\end{figure}

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Meanwhile, biochemical recurrence of PSA was intensively cer-specific survival, not tumor progression, were observed. In prostate cancer, significant improvements of overall survival and cancer drug resistant or insensitive bladder cancer existed.59 In prostate cancer, the inherent poor prognosis of bladder cancer overcomes the protective effect of statin use, or because of its intracavity. The biological behavior of bladder cancer could also be a risk for 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 cumulative 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 cancerspecific 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.

REFERENCES


FIGURE 6. Funnel plot of included studies concerning biochemical outcome following radical prostatectomy.


