

# The association of statin use and biochemical recurrence after curative treatment for prostate cancer

## A systematic review and meta-analysis

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### Abstract

**Objectives :** To investigate the association between statin use and biochemical recurrence (BCR) in patients undergoing radical prostatectomy (RP) or radiotherapy (RT) as a curative treatment, a systematic review and meta-analysis was performed.

**Methods :** We conducted a literature search of online databases for studies assessing BCR associated with statin use in patients with prostate cancer undergoing RP or RT. We performed a pooled analysis of BCR-free survival with subgroup analysis of treatment, cancer risk, and medication.

**Results :** We identified 27 studies and found that statin use was associated with a potential tendency to improve BCR-free survival in patients undergoing curative treatment ( $P = .05$ ). In addition, we revealed that statin use after curative treatment did not improve BCR-free survival ( $P = .33$ ), whereas statin use could improve BCR-free survival in high-risk patients ( $P < .01$ ).

**Conclusions :** Statin use is associated with a potential tendency to improve BCR-free survival in prostate cancer and could reduce BCR in high-risk patients.

**Abbreviations:** BCR = biochemical recurrence, HR = hazard ratio, NOQAS = Newcastle-Ottawa Quality Assessment Scale, PSA = prostate specific antigen, RCT = randomized clinical trial, RP = radical prostatectomy, RT = radiotherapy.

**Keywords:** biochemical recurrence, meta-analysis, prostate cancer, radical prostatectomy, radiotherapy, statin

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This review was based on studies published in online databases, and no newly added human samples or clinical materials were used.

This systematic review and meta-analysis was an amendment to the previous version registered in PROSPERO (CRD42020212969). Our previous search revealed that statins and their association with prostate cancer have been discussed in several reviews. However, the impact of statins on biochemical recurrence in patients undergoing curative treatment has not yet been studied, and we investigated this association in our review.

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Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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## 1. Introduction

Prostate cancer is the most commonly diagnosed malignancy in the male genitourinary system and is estimated to account for approximately 1.4 million new cases and 375 000 associated deaths worldwide in 2020.<sup>[1]</sup> Currently, radical prostatectomy (RP) and radiotherapy (RT) are both effective treatments for prostate cancer with curative intent, providing equal outcomes for tumor control.<sup>[2]</sup> However, many patients undergoing curative treatment experience prostate-specific antigen (PSA) relapse, also known as biochemical recurrence (BCR), which increases the risk of metastasis and mortality.<sup>[3]</sup> Among the various risk factors for lethal prostate cancer, recent studies have revealed that high circulating cholesterol could be associated with an increased risk of aggressive prostate cancer, while cholesterol-lowering strategies may confer protective benefit.<sup>[4]</sup> Statins, the most frequently prescribed lipid-lowering drugs that block 3-hydroxy-3-methylglutaryl coenzyme A reductase, have been shown to be inversely associated with lethal prostate cancer.<sup>[5]</sup> We learned from our preliminary search that several retrospective studies have investigated the impact of statin use on BCR in patients undergoing curative treatment, but the conclusions are inconsistent. Therefore, we performed this systematic review and meta-analysis to investigate the impact of statin use on BCR in patients undergoing RP or RT as a curative treatment for prostate cancer. Our objective was to investigate the difference in BCR risk between patients with statin use and those without such medication to assess whether statin use would reduce recurrence and progression after treatment with curative intent.

## 2. Methods

### 2.1. Search strategy and study selection

We promoted our systematic review following the guidelines of Preferred Reporting Items for Systematic reviews and Meta-Analyses and completed the registration of PROSPERO with CRD42020212969.<sup>[6]</sup> We searched for published studies evaluating BCR associated with statin use in patients undergoing RP or RT as curative treatment for prostate cancer up to December 31, 2020, in the following online databases: MEDLINE, EMBASE, and the Cochrane Central Search Library. We retrieved citations using combinations of the medical subject heading terms “prostate cancer,” “biochemical recurrence,” “prostatectomy,” “radiotherapy,” “brachytherapy,” “statin,” and “lipid-lowering drug” for medical subject heading search with the Boolean logic including “((statin) AND (prostate cancer)) AND (biochemical recurrence),” “((statin) AND (prostate cancer)) AND (prostatectomy),” “((statin) AND (prostate cancer)) AND (radiotherapy)” and “((statin) AND (prostate cancer)) AND (brachytherapy).” We also used these as keywords and text words for the freedom search. We implemented no restriction for the timing or duration of medication and different types of statins, and we also implemented no restriction for surgical approaches (open, laparoscopic, or robot-assisted RP) and radiotherapy (brachytherapy or external beam radiotherapy). Articles in languages other than English were included, whereas case reports, meeting records, and review articles were excluded. All included studies contained original data evaluating BCR associated with statin use, or these could be

calculated from the data source. Additionally, we attempted to connect the corresponding authors when the data were incomplete. Independent researchers (Peng Yin and Sheng Han) individually identified candidates for review, and senior investigators (Qingfeng Hu and Shijun Tong) made the final decision to include or exclude this review.

### 2.2. Quality assessment of included studies

We retrieved no randomized clinical trials (RCTs) investigating this issue in the search and screening and applied the Newcastle-Ottawa Quality Assessment Scale (NOQAS) to assess the quality of the included cohort studies.<sup>[7]</sup> This scale was developed to assess the quality of nonrandomized studies, with 8 items ranging from 0 to 9 in the total score, and categorized into three dimensions (selection, comparability, and outcome). A maximum of 1 point can be awarded for each item, while the comparability item allows 2 points. Additionally, we set cancer risk stratification, including Gleason score and clinical stage, as important factors to assess comparability, along with other factors, including age, PSA level, obesity, and diabetes. In addition, we considered that a median duration of >5 years would be sufficient for follow-up to detect BCR.

### 2.3. Data extraction and analysis

We aimed to assess the cumulative risk of BCR associated with statin use in patients undergoing curative treatment for prostate

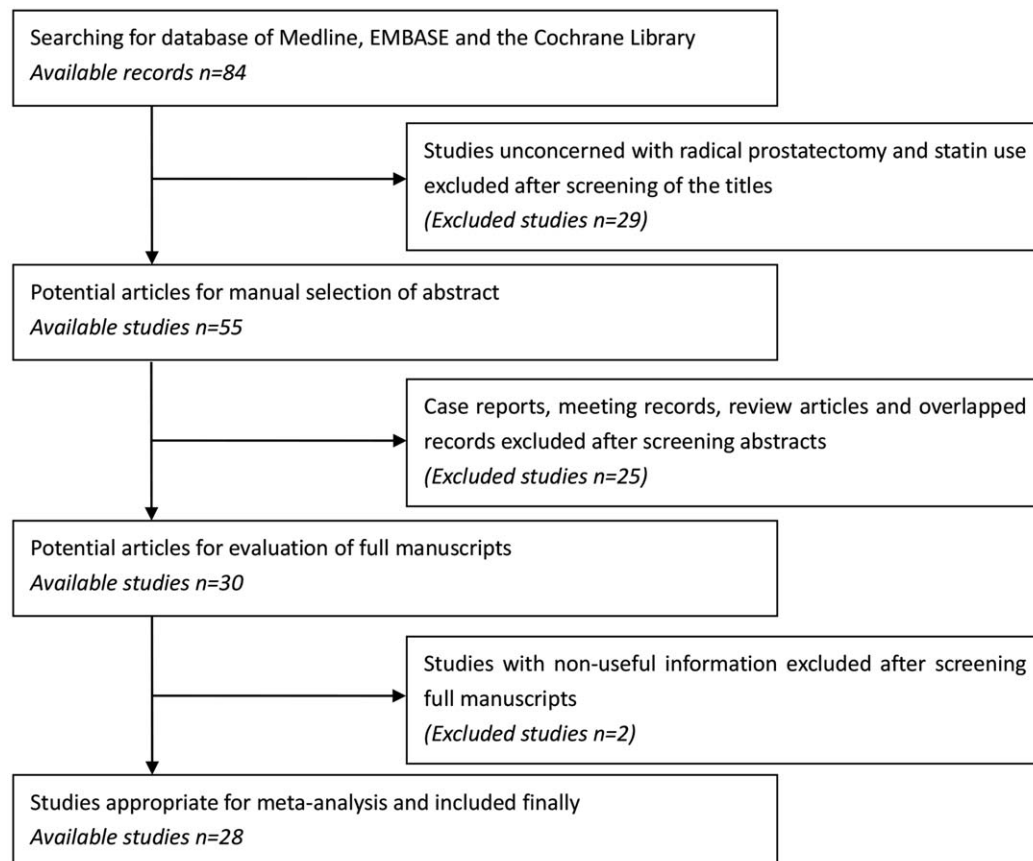


Figure 1. Flow chart of study selection and inclusion.

**Table 1****Characteristics of included studies.**

Study	Area	Treatment <sup>†</sup>	Timing <sup>‡</sup>	Statin	Nonstatin	NOS
Prabhu N. 2020	USA	RP	Both	1222	1866	7
Jarimba R. 2020	Portugal	RP	Before	320	382	5
Meijer D. 2019	Netherlands	RP	Before	252	870	5
Wettstein M.S. 2017	Switzerland	RP	Before	54	265	6
Liu X. 2017	USA	RT	Both	158	223	5
Lyon T.D. 2016	USA	RP	Before	824	2218	6
Ohno Y. 2016	Japan	RP	Before	69	493	5
Cattarino S. 2015	France	RP	Before	156	435	7
Song C. 2015	Korea	RP	After	210	1671	5
Bahig H. 2015	Canada	RT	Both	762	1010	4
Cuaron J. 2015	USA	RT	both	273	481	5
Oh D.S. 2015	USA	RT	Both	174	73	4
Ishak-Howard M.B. 2014	USA	RP	Both	258	281	7
Allott E.H. 2014	USA	RP	After	400	746	6
Rieken M. 2013	NA and EU	RP	Before	2275	4567	7
Kontraras M. 2013	Greece	RP	Both	107	481	7
Chao C.(P) 2013	USA	RP	After	654	530	6
Chao C.(R) 2013	USA	RT	Before	401	373	6
Mass A.Y. 2012	USA	RP	Before	437	1009	5
Misrai V. 2012	France	RP	Both	97	280	4
Ritch C.R. 2011	USA	RP	Before	281	980	6
Ku J.H. 2011	Korea	RP	Before	87	600	5
Kollmeier M.A. 2011	USA	RT	Both	382	1299	6
Krane L.S. 2010	USA	RP	Before	1031	2807	5
Gutt R. 2010	USA	RT	Both	189	502	6
Soto D.E. 2009	USA	RT	Both	220	748	4
Moyad M.A. 2006	USA	RT	Both	191	747	6

<sup>†</sup> RP = radical prostatectomy, RT = radiotherapy, including brachytherapy and external beam radiotherapy.

<sup>‡</sup> before = initiating statin use before treatment included, after = initiating statin use after treatment included, both = either statin use before or after treatment included.

cancer. Biochemical recurrence was defined as 2 consecutive PSA measurements  $>0.2$  ng/mL after an undetectable PSA value following the original curative therapy (RP or RT). We analyzed BCR-free survival and calculated the pooled hazard ratio (HR) using time-to-event survival data from the included studies. When HRs could not be collected directly from articles, we tried to calculate the estimated HRs according to the practical methods given by Tierney and colleagues.<sup>[8]</sup> We performed a pooled analysis comparing patients with statin use to patients without statin use, and we performed subgroup analysis for RP and RT individually. Additionally, we performed a pooled analysis for intermediate-and high-risk patients and for patients with new statin use after curative treatment. Intermediate -and high-risk patients were identified according to the D'Amico criteria.<sup>[9]</sup> When repeated data from the same cohort appeared, the most informative and recent article was selected for the analysis. Heterogeneity among studies was measured by the Cochrane  $\chi^2$ -test using the  $I^2$  metric, and the random-effects model was employed in pooled analysis considering the intention to generalize our results beyond the included studies, even though heterogeneity among studies was insignificant. It was almost impossible to assume that all studies shared a common therapeutic effect from a clinical perspective and that the random-effects model would provide a more conservative estimation. Egger's linear regression test and funnel plot were used to identify potential publication bias, and meta-analysis was abandoned when the bias was obvious. Statistical analysis was performed using STATA 16.0, and all statistical tests were 2-sided and declared significant when  $P < .05$ .

### 3. Results

We identified 27 studies for this meta-analysis, and the flow chart of the search and selection is shown in Figure 1.<sup>[10–36]</sup> Specifically, 11484 patients with statin use and 25937 patients without such medication were included; 18 studies evaluated the impact of statin use in patients undergoing RP and 9 studies evaluated the impact of statin use in patients undergoing RT. In addition, 7 studies investigated BCR risk associated with statin use in intermediate-and high-risk patients, and 5 studies compared BCR differences between patients starting statin use after curative treatment and patients without statin use. All included studies are characterized in Table 1, and we used the NOQAS to assess the quality of the included cohort studies. The results ranged from 4 to 7, with a higher score indicating a higher quality study; the three dimensions of selection, comparability, and outcome in the NOQAS are shown in Figure 2 in detail.

We revealed that statin use appeared to be associated with a potential tendency to improve BCR-free survival, although we failed to observe a significant difference (pooled HR = 0.88, 95% CI 0.77 to 1.00,  $P = .05$ ) (Fig. 3), and subgroup analysis of RP (pooled HR = 0.92, 95% CI 0.79–1.07) and RT (pooled HR = 0.78, 95% CI 0.61–1.00) also showed insignificant results. Additionally, only high-risk prostate cancer patients experienced improved BCR-free survival from statin use (pooled HR = 0.51, 95% CI 0.37–0.70,  $P < .01$ ), while an insignificant difference was observed in the subgroup analysis including both intermediate-and high-risk patients (pooled HR = 0.89, 95% CI 0.78–1.01,  $P = .08$ ) (Fig. 4). In addition, starting statin use after curative

study		selection				comparability		outcome		
		s1	s2	s3	s4	c1	c2	o1	o2	o3
Prabhu N.	2020	★	★	★	★	★	☆	★	★	☆
Jarimba R.	2020	★	★	☆	★	★	☆	★	☆	☆
Meijer D.	2019	★	★	☆	★	★	☆	★	☆	☆
Wettstein M. S.	2017	★	★	★	★	★	☆	★	☆	☆
Liu X.	2017	★	★	★	★	☆	☆	★	☆	☆
Lyon T. D.	2016	★	★	☆	★	★	☆	★	★	☆
Ohno Y.	2016	★	★	★	★	☆	☆	★	☆	☆
Cattarino S.	2015	★	★	★	★	★	★	★	☆	☆
Song C.	2015	★	★	★	★	☆	☆	★	☆	☆
Bahig H.	2015	★	★	☆	★	☆	☆	★	☆	☆
Cuaron J.	2015	★	★	★	★	☆	☆	★	☆	☆
Oh D. S.	2015	☆	★	★	★	☆	☆	★	☆	☆
Ishak-Howard M. B.	2014	★	★	★	★	★	☆	★	★	☆
Allott E. H.	2014	★	★	★	★	☆	☆	★	★	☆
Rieken M.	2013	★	★	★	★	★	★	★	☆	☆
Kontraros M.	2013	★	★	★	★	★	★	★	☆	☆
Chao C. (P)	2013	★	★	★	★	★	☆	★	☆	☆
Chao C. (R)	2013	★	★	★	★	★	☆	★	☆	☆
Mass A. Y.	2012	★	★	★	★	☆	☆	★	☆	☆
Misrai V.	2012	☆	★	★	★	☆	☆	★	☆	☆
Ritch C. R.	2011	★	★	★	★	★	☆	★	☆	☆
Ku J. H.	2011	☆	★	★	★	★	☆	★	☆	☆
Kollmeier M. A.	2011	★	★	★	★	☆	☆	★	★	☆
Krane L. S.	2010	★	★	★	★	☆	☆	★	☆	☆
Gutt R.	2010	★	★	★	★	★	☆	★	☆	☆
Soto D. E.	2009	★	★	☆	★	☆	☆	★	☆	☆
Moyad M. A.	2006	★	★	☆	★	★	☆	★	★	☆

Figure 2. Characteristics of NOS for included studies.

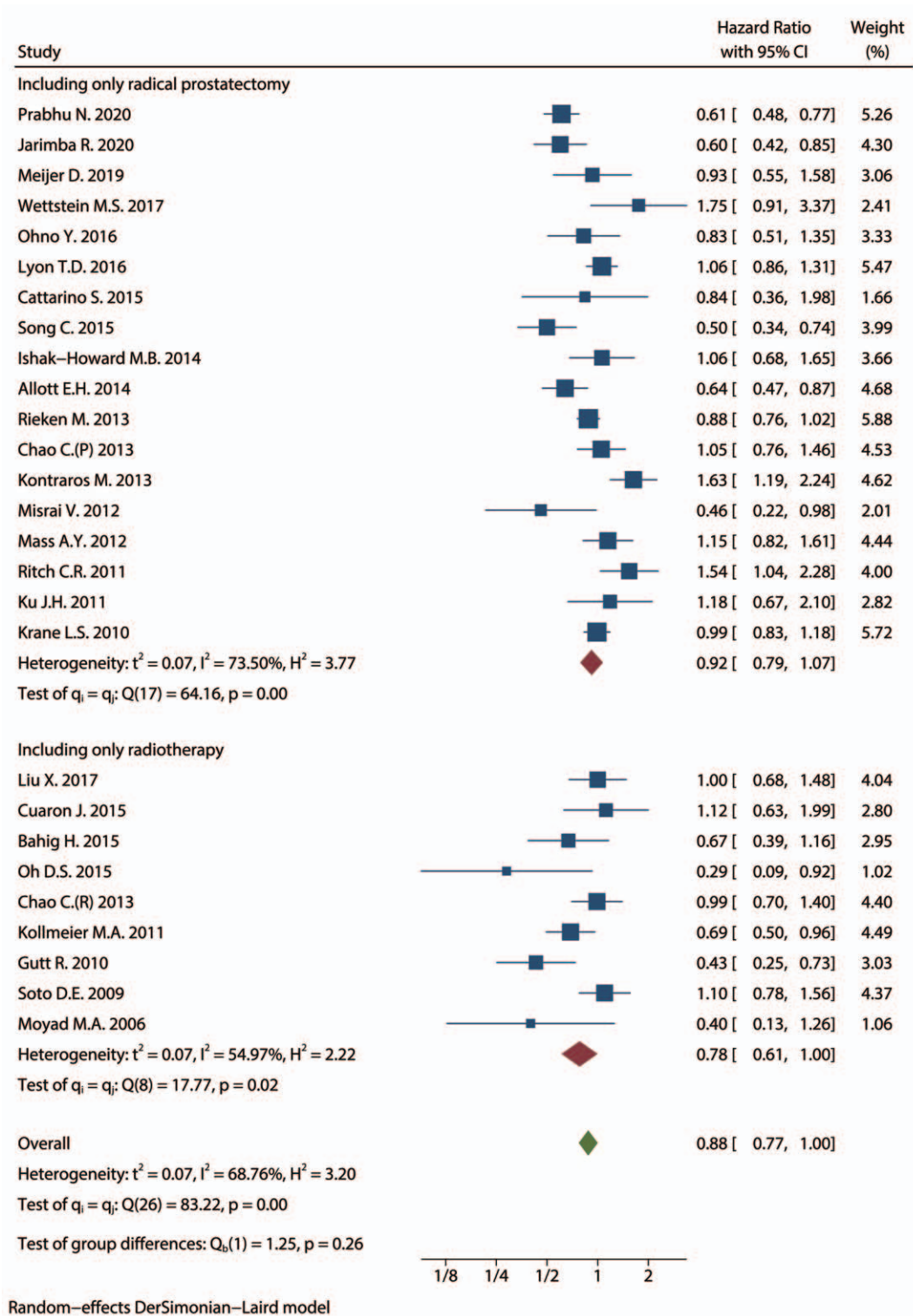
treatment did not improve BCR-free survival (pooled HR=0.85, 95% CI 0.62–1.18,  $P=.33$ ) (Fig. 5). No publication bias was observed in the funnel plot or Egger test.

#### 4. Discussion

Although previous studies have evaluated the potential improvement of statin use for progression and mortality in patients with prostate cancer, it is still controversial whether statin use would reduce BCR in patients undergoing RP or RT as curative treatment.<sup>[37–39]</sup> Therefore, in this systematic review and meta-analysis, we investigated the risk of BCR associated with statin use. We revealed that statin use appeared to be associated with a potential tendency to improve BCR-free survival; however, we failed to find significant differences, and subgroup analysis of RP and RT also showed insignificant results. Moreover, statin use after curative treatment did not improve the BCR-free survival.

However, only high-risk patients with prostate cancer experience improved BCR-free survival following statin use. Our results would be valuable for further research to reduce recurrence and improve the survival of prostate cancer patients, especially when more prostate cancer patients can be detected at an early stage and curative treatment strategies are currently possible and effective.

Statins are specific inhibitors of the mevalonate pathway, which is responsible for the de novo synthesis of cholesterol and non-sterol isoprenoids, and have been accepted as the most effective treatment in the clinical management of high lipids and high cholesterol. Moreover, in addition to the association between obesity and cancer, dysregulation of the mevalonate pathway can support tumorigenesis and progression.<sup>[40,41]</sup> Therefore, interest is emerging in repurposing statins as anticancer agents, similar to prostate cancer. Although most men are diagnosed with organ-confined prostate cancer in clinics,



**Figure 3.** Overall and subgroup analysis comparing BCR-free survival in patients with ever statin use compared to those with never statin use using the random-effects model.

long-term oncological outcomes can vary greatly, indicating the diversity of clinical, morphological and molecular characteristics.<sup>[42]</sup> In contrast to other encouraging results, we have revealed that statin use appeared to be only associated with a

potential tendency to improve BCR-free survival, although we failed to find a significant difference. In addition, patients who started statin use after curative treatment did not show improved BCR. The only positive outcome was that statin use would

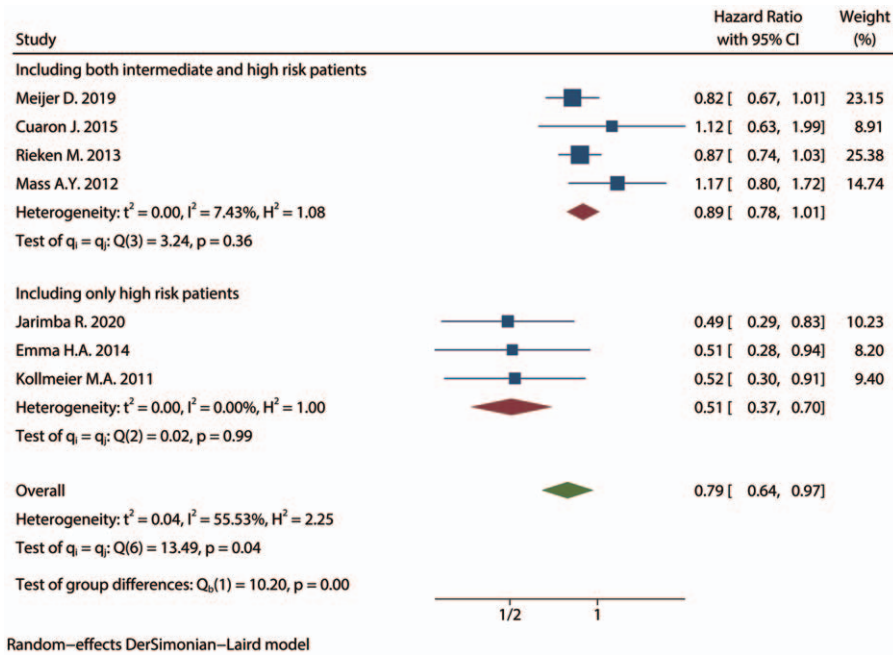


Figure 4. Pooled analysis comparing BCR-free survival in intermediate and high risk patients.

improve BCR-free survival in high-risk prostate cancer patients, and such improvement might involve a distinctive molecular or metabolic mechanism for the special subtype. An interesting issue is the potential tendency for statin use to improve BCR-free survival in patients undergoing RT instead of RP. Currently, the combination of RT and ADT has definitively proven its superiority compared with RT alone on recurrence by various RCTs,<sup>[43–45]</sup> while statin use combined with ADT would prolong time to progression, and statin could competitively reduce androgen uptake in vitro.<sup>[46]</sup> Therefore, statins may reinforce the effect of ADT in combination with RT.

Finally, the limitations of our meta-analysis should be reviewed and considered before interpreting our results. First, no RCT is available, and baseline imbalances are inevitable, even in well-designed cohort studies. Patients using statins might return to

clinics more frequently, and BCR might be detected earlier. Statin use might be related to obesity, diabetes, or other metabolic disorders, which are also risk factors for the incidence and mortality of prostate cancer.<sup>[47]</sup> Second, it is difficult to collect and administer medication information accurately about timing, duration, drug types, and alterations, which would bring about confounding and bias. Moreover, the random effects model is accepted in our analysis because each study estimates a different underlying true effect instead of 1 common effect, and we would like to generalize extensive inference, not only to focus on difference or *P* value. However, the insufficient quantity and heterogeneity of studies would still reduce the reliability of statistical inferences. Therefore, it is important to interpret our results critically, and more well-designed studies with larger samples are needed to provide a robust conclusion.

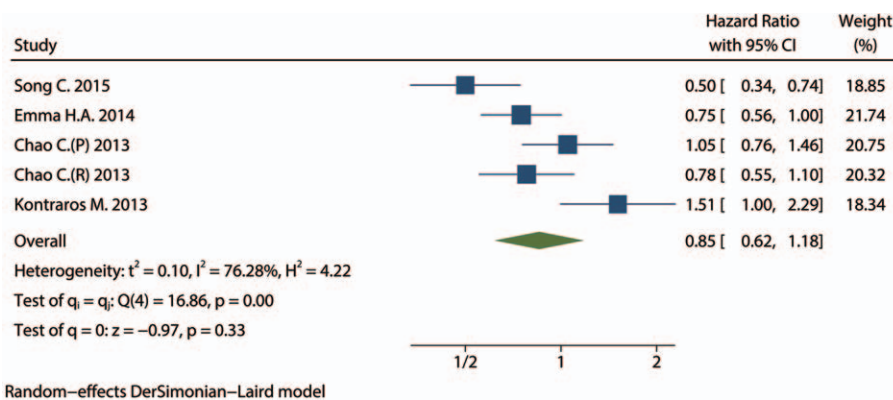


Figure 5. Pooled analysis comparing BCR-free survival in patients with statin use after curative treatment compared to those without statin use.

In conclusion, statin use is associated with a potential tendency to improve BCR-free survival in prostate cancer and could reduce BCR in high-risk patients.

## Author contributions

**Investigation:** Peng Yin.

**Resources:** Peng Yin.

**Software:** Sheng Han, Qingfeng Hu, Shijun Tong.

**Supervision:** Qingfeng Hu, Shijun Tong.

**Writing – original draft:** Peng Yin.

**Writing – review & editing:** Qingfeng Hu.

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