Statins and prostate cancer recurrence following radical prostatectomy or radiotherapy: a systematic review and meta-analysis

H. S. Park1,2,3,†, J. D. Schoenfeld1,4,†, R. B. Mailhot1,5, M. Shive1,6, R. I. Hartman1,7, R. Ogembo1,8 & L. A. Mucci1

1Department of Epidemiology, Harvard School of Public Health, Boston; 2Department of Internal Medicine, Beth Israel Deaconess Medical Center, Boston; 3Department of Therapeutic Radiology, Yale School of Medicine, New Haven; 4Harvard Radiation Oncology Program, Boston; 5School of Medicine, Washington University in St. Louis, St. Louis; 6School of Medicine, University of California, San Francisco; 7Perelman School of Medicine, University of Pennsylvania, Philadelphia; 8Northeastern University, Boston, USA

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Background: In this meta-analysis, we evaluated associations between statins and recurrence-free survival (RFS) following treatment of localized prostate cancer, with attention to potential benefits among patients treated primarily with radiotherapy (RT) versus radical prostatectomy.

Patients and methods: We identified original studies examining the effect of statins on men who received definitive treatment of localized prostate cancer using a systematic search of the PubMed and EMBASE databases through August 2012. Our search yielded 17 eligible studies from 794 references; 13 studies with hazard ratios (HRs) for RFS were included in the formal meta-analysis.

Results: Overall, statins did not affect RFS (HR 0.90, 95% CI 0.74–1.08). However, in RT patients (six studies), statins were associated with a statistically significant improvement in RFS (HR 0.68; 95% CI 0.49–0.93); this benefit was not observed in radical prostatectomy patients (seven studies). Sensitivity analyses suggested that primary treatment modality may impact the effect of statins on prostate cancer recurrence.

Conclusions: Our meta-analysis suggests a potentially beneficial effect of statins on prostate cancer patients treated with RT but not among radical prostatectomy patients. Although limited by the lack of randomized data, these results suggest that primary treatment modality should be considered in future studies examining associations between statins and oncologic outcomes.

Key words: meta-analysis, prostate cancer, radical prostatectomy, radiotherapy, recurrence, statin

introduction

Statins or 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors are widely used treatments for hypercholesterolemia. However, by inhibiting cholesterol synthesis, statins also inhibit the production of farnesyl pyrophosphate and geranylgeranyl pyrophosphate, two biochemical products essential for cell growth and proliferation [1, 2]. These and other potential anti-proliferative and pro-apoptotic properties suggest that statins could also inhibit carcinogenesis and impact cancer outcomes [3]. Indeed, one large, population-based study recently demonstrated an association between statin use and reduced cancer-specific mortality across multiple cancer subtypes [4].

The effect of statin use on prostate cancer, in particular, is of interest given the overlapping demographics of this malignancy and hypercholesterolemia as well as the high prevalence of statin use (~24 million Americans in 2003–2004 [5]). Since both diseases commonly afflict older men, many prostate cancer patients are already prescribed statins at the time of their cancer diagnosis and treatment. Previous studies that have examined the association of statin use with prostate cancer incidence have reached variable conclusions [6–10]. Meta-analyses examining this association have been also equivocal [11–16].

Several studies have found an inverse association between statin use and decreased incidence of more aggressive disease, defined as high grade or advanced disease [8, 11, 17]. Moreover, statins may also impact prostate cancer outcomes after definitive treatment; by targeting cholesterol synthesis,
statins may decrease prostate cancer’s ability to synthesize testosterone de novo and impede progression to metastatic disease [18, 19]. Recent observational studies have explored whether statins may have a role in reducing progression after diagnosis. However, these analyses were ill-equipped to evaluate the potentially modifying effects of primary treatment as most only examined outcomes following either radical prostatectomy or radiation therapy. Both radical prostatectomy and radiation therapy (either external beam or brachytherapy) are commonly employed as definitive treatment modalities for early-stage prostate cancer, and outcomes after each treatment may be affected by statin use differentially, especially given the hypothesis that statins may act as radiosensitizers [3]. As has been observed with androgen deprivation therapy, an adjuvant treatment that impacts outcome after radiotherapy (RT) may not affect the outcome after radical prostatectomy [20–22]. Thus, in order to comprehensively evaluate the association of statin use with prostate cancer recurrence and the potentially modifying effects of primary treatment, we undertook a meta-analysis of the available data.

**Methods**

**Search Methods**

Search terms were designed by five authors (JDS, HP, RM, MS and RO) to include all studies that investigated the association of statin use with prostate cancer outcomes, using all relevant synonyms for prostate cancer, genitourinary malignancies, and both trade and generic drug names for all statins in clinical use. These search terms are fully detailed in the Appendix. The search was applied to PubMed (1965 to present) and EMBASE (1974 to present), with the last search run on 2 August 2012. All publications, including abstracts, were eligible for retrieval, with duplicate publications removed. In addition, six authors (JDS, HP, RM, MS, RH and RO) conducted a manual review of the reference sections of the retrieved articles in order to identify additional relevant studies.

**Selection Criteria**

All unpublished, published, in press, and in progress studies were initially targeted for review if they were identified in the PubMed or EMBASE search, reported primary data and investigated the association between statins and outcomes after diagnosis among men with initially localized, non-metastatic prostate cancer. Both full-text articles and abstracts were eligible. Epidemiological studies that did not report disease outcomes after diagnosis such as mortality, biochemical failure and disease-specific mortality according to statin use were excluded. Studies including metastatic prostate cancer patients at diagnosis or non-human subjects were also excluded. Language selection was limited to articles written in English, Spanish, Italian, Portuguese and French. Each citation was assessed for inclusion independently by at least two out of six authors (JDS, HP, RM, MS, RH and RO), and any discrepancies were arbitrated by all authors. In studies that recorded outcomes for similar or overlapping cohorts, data from the publication with the longest follow-up time were utilized.

**Data Extraction and Analysis**

Two independent reviewers extracted data from each study. Hazard ratio (HR) effect estimates were used to assess potential associations between statin use and prostate cancer recurrence following treatment. Biochemical recurrence-free survival (RFS) estimates were used when available; however, progression-free survival estimates were also utilized if biochemical data were not reported separately. We attempted to contact study authors by e-mail to obtain these data if not available from the published reports. Adjusted multivariate estimates were used in all cases. In one study [23], the multivariate result obtained by personal communication was discordant with the univariate analysis; these data were verified before inclusion. Summary HR measurements were calculated with 95% confidence intervals (CIs) using both fixed-effects and DerSimonian and Laird random-effects modeling, which accounted for both within-study and between-study variation [24]. The standard error of the HRs was determined by dividing the difference of the upper and lower 95% CI values on the log scale by 3.92 (twice the value of the z-score for the 95% CI) [25]. We used Cochran’s Q test to test for heterogeneity between studies, with a P value <0.10 considered statistically significant [26]. We also used the I² test to quantify the proportion of total variation across studies due to heterogeneity rather than chance [27, 28]. Negative values of I² were set to zero, so that I² resided between 0 and 100%. Potential sources of heterogeneity were explored through stratification by primary treatment modality (prostatectomy versus radiation therapy), random-effects meta-regression modeling, inference analysis and exclusion sensitivity analyses. Publication bias was evaluated using the Begg and Mazumdar adjusted rank correlation test and Egger’s regression asymmetry test [29, 30]. All P values were two-tailed with α = 0.05 to establish statistical significance.

This work was carried out in accordance with the guidelines proposed by the Meta-Analysis of Observational Studies in Epidemiology group [31] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) group [32]. STATA 11.1 was used to conduct all statistical analyses (STATA, College Station, TX).

**Results**

**Study Characteristics**

Our initial search yielded 794 citations (Figure 1). Of these, 769 were deemed to be irrelevant based on the title and/or abstract review, leaving 25 cohort studies for full article review. Additional reasons for exclusion following full-text review included: inseparable analysis of prostate cancer incidence (two studies) [8, 33], a population comprised of patients diagnosed with metastatic prostate cancer [34] or utilization of an identical or subset of patients analyzed in another publication with longer follow-up (five studies) [23, 35–38]. Characteristics of the 17 remaining studies are shown in Table 1. Four of these studies were excluded from further
In this comprehensive meta-analysis among men following definitive treatment of localized prostate cancer, we found no overall association between statin use and recurrence. In a planned subgroup analysis of studies by treatment modality, there was no association with statin use and recurrence among men who underwent radical prostatectomy as primary therapy. In contrast, among men for whom RT was the primary treatment modality, there was a statistically significant 32% lower risk of recurrence among statin users. Furthermore, after excluding the surgical study that contained a significant proportion of irradiated patients, there was a statistically significant difference in effect estimates for statins by treatment modality. Meta-regression failed to demonstrate significant effects of study characteristics, including publication type, total sample size and publication year on the outcome. To our knowledge, this is the first meta-analysis to address this topic.

A benefit of statin use limited to patients treated with RT could potentially be explained by statin-induced radiosensitizing effects. The combination of statins and ionizing radiation has been shown to increase prostate cancer cell death in both in vitro and in vivo models [18, 52, 55]. One postulated mechanism for this radiosensitization involves the MYC oncogene, as statins in combination with radiation increase cancer cell death while decreasing cellular MYC levels in vitro [55].

The addition of the HMG-CoA bypass product

quantitative data synthesis

In most studies, the prevalence of statin use ranged from 20 to 35%, although it was 70% in the study by Oh et al. [53]. Overall, there was no association between statin use and recurrence after prostate cancer diagnosis [HR 0.90, 95% CI 0.74–1.08] (Figure 2). The association was null among the men who underwent radical prostatectomy as primary therapy (HR = 1.05, 95% CI 0.90–1.24). However, among men who underwent radiation therapy as the primary treatment, statin users had a statistically significantly lower risk of recurrence compared with non-users (HR 0.68; 95% CI 0.49–0.93).

There was no clear evidence of publication bias found on the funnel plot (Figure 3), the Begg rank correlation method (P = 0.807) or the Egger weighted regression method (P = 0.624). There was evidence of significant heterogeneity overall (I² = 69.6%, P = 0.001) and in studies including RT patients only (I² = 63.2%, P = 0.018). Meta-regression investigating potential sources of heterogeneity demonstrated that primary treatment modality, publication type (complete manuscript versus abstract), total sample size and publication year were not significantly associated with lower risk of recurrence (data not shown). Among RT studies, the use of androgen deprivation therapy also did not significantly influence the association between statin use and recurrence.

We undertook sensitivity analyses to test the robustness of our results. Fixed-effects models were consistent with random-effects models, showing that statin use was not associated with recurrence among all studies (HR 0.92, 95% CI 0.84–1.01), but was associated with significantly decreased recurrence in patients treated primarily with RT (HR 0.70, 95% CI 0.59–0.83). Inference analyses omitting any one publication did not significantly change the overall treatment-specific summary estimate for radical prostatectomy or RT studies. However, omitting Hamilton et al. [43], in which 26% of the RP patients also received adjuvant RT, led to a significant effect modification of treatment modality on the association between statins and recurrence (P = 0.043).

discussion

In this comprehensive meta-analysis among men following definitive treatment of localized prostate cancer, we found no overall association between statin use and recurrence. In a planned subgroup analysis of studies by treatment modality, there was no association with statin use and recurrence among men who underwent radical prostatectomy as primary therapy. In contrast, among men for whom RT was the primary treatment modality, there was a statistically significant 32% lower risk of recurrence among statin users. Furthermore, after excluding the surgical study that contained a significant proportion of irradiated patients, there was a statistically significant difference in effect estimates for statins by treatment modality. Meta-regression failed to demonstrate significant effects of study characteristics, including publication type, total sample size and publication year on the outcome. To our knowledge, this is the first meta-analysis to address this topic.
mevalonate reverses both the increased cancer cell death and decreased MYC levels [55]. Statin use may also promote autophagy pathways that play a synergistic role with radiation in promoting prostate cancer cell death [56].

Given the antineoplastic properties previously attributed to statins, the lack of benefit of statin use on prostate cancer recurrence in patients treated with radical prostatectomy is somewhat unexpected. Statins' antineoplastic effects may be context-dependent, and therefore, may be subtle or even nonexistent in the setting of radical prostatectomy. Such differential benefit by treatment modality has been observed for adjuvant androgen-deprivation therapy; no consistent benefit has been observed following radical prostatectomy, although a clear survival benefit exists in the setting of RT [20, 21, 57]. Although radiation was not a significant modifier of the association between statin use and cancer-specific mortality in a recently published analysis [4], this study included a heterogeneous variety of cancer types and many patients who were likely treated in the metastatic setting. Furthermore, the data on treatment with chemotherapy or RT were missing in up to 72% of patients [58].

Our findings should be interpreted in light of several factors. First, the available literature was limited to observational cohort studies, which may be subject to bias and confounding.

Table 1. Study characteristics of all extracted studies of the association between statin use and outcomes after prostate cancer diagnosis

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of patients</th>
<th>No. of patients on statins (%)</th>
<th>Primary treatment(s) received</th>
<th>ADT</th>
<th>Outcome(s) with use of statins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alizadeh et al. [42]*</td>
<td>381</td>
<td>172 (45%)</td>
<td>Radiotherapy (RT): EBRT (58%) or brachytherapy (42%)</td>
<td>24%</td>
<td>Odds ratio for PSA&gt;20: 0.29 (0.08–0.83)*</td>
</tr>
<tr>
<td>Gutt et al. [52]</td>
<td>691</td>
<td>189 (27%)</td>
<td>RT: EBRT</td>
<td>41%</td>
<td>Hazard ratio (HR) for BR: 0.43 (0.25–0.73)*</td>
</tr>
<tr>
<td>Hamilton et al. [43]</td>
<td>1319</td>
<td>236 (18%)</td>
<td>Radical prostatectomy + 26% with adjuvant RT</td>
<td>18%</td>
<td>HR for BR: 0.70 (0.50–0.97)*</td>
</tr>
<tr>
<td>Katz et al. [39]*</td>
<td>7042</td>
<td>1824 (26%)</td>
<td>65% Radical prostatectomy only with 35% RT only</td>
<td>41%</td>
<td>HR for ACM: Radical prostatectomy patients: 0.35 (0.21–0.58)* RT patients: 0.59 (0.37–0.94)*</td>
</tr>
<tr>
<td>Kollmeier et al. [10]</td>
<td>1681</td>
<td>382 (23%)</td>
<td>RT: EBRT</td>
<td>56%</td>
<td>HR for BR: 0.69 (0.50–0.97)*</td>
</tr>
<tr>
<td>Krane et al. [44]</td>
<td>3828</td>
<td>1031 (27%)</td>
<td>Radical prostatectomy</td>
<td>NR</td>
<td>HR for BR: 0.99 (0.83–1.18)*</td>
</tr>
<tr>
<td>Ku et al. [46]</td>
<td>609</td>
<td>79 (13%)</td>
<td>Radical prostatectomy</td>
<td>0%</td>
<td>HR for BR: 1.18 (0.67–2.10)*</td>
</tr>
<tr>
<td>Lavery et al. [40]*</td>
<td>1642</td>
<td>521 (32%)</td>
<td>Radical prostatectomy</td>
<td>NR</td>
<td>HR for BR: not significant</td>
</tr>
<tr>
<td>Mass et al. [49]</td>
<td>1446</td>
<td>437 (30%)</td>
<td>Radical prostatectomy</td>
<td>0%</td>
<td>HR for BR: 1.15 (0.82–1.61)*</td>
</tr>
<tr>
<td>Mondul et al. [47]</td>
<td>2398</td>
<td>386 (16%)</td>
<td>Radical prostatectomy</td>
<td>0%</td>
<td>HR for any recurrence: 1.00 (0.67–2.10)*</td>
</tr>
<tr>
<td>Moyad et al. [50]</td>
<td>938</td>
<td>191 (20%)</td>
<td>RT: brachytherapy + 57% with supplemental EBRT</td>
<td>41%</td>
<td>BR within 9 years: 1.6% (statins) versus 4.8%, log-rank P = 0.06 DSM within 9 years: 0% (statins) versus 4.1%, log-rank P = 0.12 ACM within 9 years: 14.2% (statins) versus 22.8%, log-rank P = 0.787 HR for BR: 1.50 (0.33–6.94)*d</td>
</tr>
<tr>
<td>Oh et al. [53]*</td>
<td>247</td>
<td>174 (70%)</td>
<td>RT: brachytherapy + 10% with supplemental EBRT</td>
<td>26%</td>
<td>HR for BR: 0.29 (0.09–0.89)*</td>
</tr>
<tr>
<td>Rioja et al. [45]*</td>
<td>3748</td>
<td>1084 (29%)</td>
<td>Radical prostatectomy</td>
<td>0%</td>
<td>HR for BR: 1.15 (0.89–1.50)*</td>
</tr>
<tr>
<td>Ritch et al. [48]</td>
<td>1261</td>
<td>281 (22%)</td>
<td>Radical prostatectomy</td>
<td>0%</td>
<td>HR for BR: 1.54 (1.0–2.2)*</td>
</tr>
<tr>
<td>Sharma et al. [41]*d</td>
<td>914</td>
<td>264 (29%)</td>
<td>RT: EBRT</td>
<td>0%</td>
<td>HR for BR: 0.783* P = 0.35*; 1.1016*, P = 0.94* HR for DSM: 2.747*, P = 0.25*; 2.365*, P = 0.32* HR for ACM: 0.186*, P = 0.001*; 1.032*, P = 0.90*</td>
</tr>
<tr>
<td>Soto et al. [51]</td>
<td>968</td>
<td>220 (23%)</td>
<td>RT: EBRT</td>
<td>29%</td>
<td>HR for any recurrence: 1.1 (0.8–1.6)*</td>
</tr>
<tr>
<td>Zaorsky et al. [54]</td>
<td>2051</td>
<td>691 (34%)</td>
<td>RT: EBRT</td>
<td>0%</td>
<td>BR within 18 months: 3.3% (statins) versus 11.4% Odds ratio for BR within 18 months: 0.41 (0.25–0.65) HR for BR: 0.63 (0.49–0.82)*</td>
</tr>
</tbody>
</table>

*Excluded from formal meta-analyses due to lack of extractable, comparable data specific to the hazard of first recurrence based on any statin use.
*bAbstract only.
*cMultivariate adjusted effect estimate.
*dObtained by correspondence with primary authors.
*ePost-RT statin use only.
*fPre-RT statin use only.

ADT, androgen deprivation therapy; EBRT, external beam RT; BR, biochemical recurrence; NR, not reported; ACM, all-cause mortality; DSM, disease-specific mortality.
although we used multivariate adjusted HRs to account for this potential source of bias. Second, there was significant heterogeneity among studies that may reflect the different methodologies and patient characteristics of the studies included. We sought to address this problem by using random-effects modeling to attenuate the impact of this heterogeneity on the validity of the pooled results. Third, we excluded four studies that addressed our study question but failed to report a unified effect estimate for recurrence as a function of peri-treatment statin use. Since these studies were not included in our quantitative analysis, the power and precision of our results were likely reduced. Indeed, in line with our current findings, among the studies that were excluded due to their lack of a unified effect estimate for statin use on RFS, one reported a non-significant effect of statins on biochemical recurrence among men treated with radical prostatectomy [40]. The other three excluded studies either reported only on all-cause mortality [39] or PSA at diagnosis [42], or further subdivided outcome based on the timing of statin use [41], making direct comparisons with other studies impossible.

Despite these limitations, carrying out a meta-analysis allowed us to compare associations between statin use and prostate cancer recurrence in patients treated with radical prostatectomy with the effect of statins on patients treated with RT. In contrast, previous individual studies reported in the literature were predominantly limited to a single-definitive modality, and therefore could not investigate effect modification due to treatment type. There was no clear evidence of publication bias, which is unsurprising given our broad search criteria and inclusion of abstracts unaccompanied by complete manuscripts. Our subgroup analysis demonstrated a differential effect of statins on RFS in patients treated with

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**Figure 2.** Meta-analysis of studies investigating association of statins with recurrence-free survival (RFS), stratified by primary treatment modality. Hazard ratios (HRs) and 95% confidence intervals (CIs) are reported on a logarithmic scale. Pooled estimates are from a random-effects model. RT, radiotherapy; RP, radical prostatectomy.

**Figure 3.** Publication bias assessed by the funnel plot.
RT when compared with radical prostatectomy. This suggests that associations between statin use and prostate cancer outcomes are less likely to be due to statins’ potential ability to artificially lower PSA levels as has been suggested previously [59, 60], as such an artifactual effect of statins would uniformly decrease recurrence in both prostatectomy and RT patients.

In summary, our meta-analysis demonstrates that statin use is not associated with a significant effect on recurrence among all patients definitively treated for prostate cancer. Intriguingly, a benefit was noted in patients primarily treated with RT; this observation somewhat reconciles the seemingly disparate and conflicting results noted in prior observational studies on statin use and prostate cancer recurrence. Though the results of this meta-analysis should be approached with caution due to the inherent biases of observational studies and the lack of randomized, controlled trials, our results suggest that treatment modality should be considered a factor in future studies examining the association of statins with prostate cancer outcomes. Since widespread use of statins has led to the identification of unexpected potential long-term side-effects such as diabetes [61], it is even more important to identify those subsets of patients most likely to benefit from an antineoplastic effect in future confirmatory, randomized studies.

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disclosure

The authors have declared no conflicts of interest.

references

Male breast cancer: risk factors, biology, diagnosis, treatment, and survivorship

K. J. Ruddy* & E. P. Winer
Medical Oncology, Dana-Farber Cancer Institute, Boston, USA

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Background: The causes, optimal treatments, and medical/psychosocial sequelae of breast cancer in men are poorly understood.

Design: A systematic review of the English language literature was conducted to identify studies relevant to male breast cancer between 1987 and 2012 and including at least 20 patients. Searches were carried out on PubMed using the title terms ‘male breast cancer’ or ‘male breast carcinoma’.

Results: Relevant published data regarding risk factors, biological characteristics, presentation and prognosis, appropriate evaluation and treatment, and survivorship issues in male breast cancer patients are presented. BRCA2 mutations, age, conditions that alter the estrogen/androgen ratio, and radiation are proven risk factors. Disease biology is distinct in men, but diagnostic approaches and treatments for men are generally extrapolated from those in women due to inadequate research in men. Survivorship issues in men may include sexual and hormonal side-effects of endocrine therapies as well as unique psychosocial impacts of the disease.

Conclusion: Further research is needed to address gaps in knowledge pertaining to care of male breast cancer patients and survivors.

Key words: breast neoplasms, drug therapy, etiology, male, survivors

Introduction

Researchers have focused relatively little attention on male breast cancer compared with female breast cancer. While only 0.5%–1% of all breast cancers in the United States occur in men, approximately 2000 men are diagnosed with breast cancer annually, and the incidence appears to be slowly rising [1–5]. Men are approximately as likely to be diagnosed with breast cancer as to develop chronic myelogenous leukemia. Because robust clinical evidence is lacking, treatment standards for men have generally been extrapolated from the enormous literature and clinical experience in women. However, these data may not be entirely applicable to men. The male hormonal milieu may be a unique and powerful determinant of risk, prognosis, and treatment outcome. Moreover, gender differences may affect patient preferences, toxic effects from therapies, and survivorship priorities. The purpose of this review is to examine systematically all recent published data regarding risk factors, biological characteristics, presentation and prognosis, appropriate evaluation and treatment, and survivorship issues in male breast cancer patients.

Methodology

A systematic review of the English language literature was conducted to identify studies relevant to male breast cancer between 1987 and 2012 and including at least 20 patients. Searches were carried out on PubMed using the title terms ‘male breast cancer’ or ‘male breast carcinoma’. Of 723 articles generated by these search terms, 340 were case reports or case series that included fewer than 20 patients, 82 were reviews or editorials,