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The association between statin medication and progression after surgery for localized renal cell carcinoma

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Abstract

Purpose—Evidence suggests statins may influence pathways of RCC proliferation, though no study has examined the influence of statin medications on progression of RCC in humans.

Materials and Methods—We identified 2608 patients with localized RCC who were treated surgically between 1995–2010 at our tertiary referral center. Competing risks Cox proportional hazards models were used to evaluate the relationship between statin use and time to local recurrence or progression (metastases or death from RCC) and overall survival. Statin use was modeled as a time-dependent covariate as a sensitivity analysis. Models were adjusted for clinical and demographic features.

Results—Of 2608 patients, 699 (27%) were statin users at surgery. Statin users had similar pathological characteristics compared to nonusers. With a median follow-up of 36 months, there were 247 progression events. Statin use was associated with a 33% reduction in the risk of progression after surgery (HR 0.67, 95% CI 0.47–0.96, p=0.028) and an 11% reduction in overall mortality that was not significant (HR 0.89, 95% CI 0.71–1.13, p=0.3). Modeling statin use as time-dependent covariate attenuated the risk reduction in progression to 23% (HR 0.77, p=0.12) and augmented the risk reduction in overall survival (HR 0.71; p=0.002).

Conclusions—In our cohort, statin use was associated with a reduced risk of progression and overall mortality, though this effect was sensitive to method of analysis. If validated in other

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cohorts, this finding warrants consideration of prospective research on statins in the adjuvant setting.

Keywords

Kidney neoplasms; hydroxymethylglutaryl-CoA reductase inhibitors; nephrectomy; disease progression; chemoprevention

Introduction

Despite localized disease at initial treatment for renal cell carcinoma (RCC), approximately 10% of patients will progress after surgery and the majority of those who do will die of the disease.[1–3] Currently there are no approved therapies to reduce the risk of recurrence, progression, or death from RCC after treatment of localized (N0M0) disease.

Statins have antineoplastic properties, including the ability to promote apoptosis and inhibit inflammation, angiogenesis, cell proliferation, migration/adhesion, invasion.[4–7] However, clinical evidence supporting an antineoplastic role for statins is encouraging but often conflicting.

The role of statins in RCC has not been studied thoroughly. Though laboratory evidence is encouraging,[8,9] only 3 clinical studies have examined the association between statins and RCC incidence. A nested case-control study of nearly 500,000 veterans observed statin use was associated with a 48% reduction in the risk of RCC.[10] In a combination study of two large prospective cohorts, statin use was protective in women but not men.[11] A third case-control study found no association.[12]

In the only laboratory study to examine statins and RCC progression, fluvastatin inhibited in vitro invasive properties, angiogenesis and decreased progression of Renca xenografts to lung metastases in mice.[9] To date, no human study has explored the influence of statins on RCC progression. We examined the relationship between statins and progression after surgery for localized (N0M0) RCC.

Materials and Methods

Study Population

With Institutional Review Board approval, we identified 2,608 patients with localized (N0M0) RCC treated with partial or radical nephrectomy between 1995–2010 at Memorial Sloan-Kettering Cancer Center. Patients treated earlier were excluded as statin use was rare then. Patients with known familial RCC syndromes were also excluded to reduce heterogeneity.

Medical records were reviewed and detailed information on statin initiation and cessation, type, dose, and duration were collected. Fuhrman grade was not routinely assigned for non-clear cell histology. Clinical stage was not available for all patients and thus was not used in this analysis; however, pathological stage was available for all patients.

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Follow-up

Follow-up consisted of clinical visits every 6 months with history, physical exam, comprehensive metabolic panel, abdominal computerized tomography (CT) or ultrasound, and chest x-ray or chest CT. After 3 years recurrence-free, follow-up was lengthened to yearly intervals. Local recurrence was considered if new growth was detected in the surgical bed >3 months after surgery. Contralateral second primary tumors were not counted as local recurrences. Progression was classified as metastases or death from RCC. The date of death was considered the date of progression for patients who died from RCC before documentation of metastases (n=34).

Statistical Analysis

The primary aim was to investigate the difference in probability of progression and overall mortality between patients who used statins and those that did not at the time of surgery. Due to the high rate of death from other causes, competing risk regression was used to compare progression risk between statin users and nonusers at surgery with death from other causes as the competing risk. Differences in overall mortality were analyzed using Cox proportional hazards model. The two outcomes were examined separately in models adjusted for demographic, clinical, preoperative, and pathologic variables known to be associated with statin use or progression and mortality: age(continuous), gender (male/female), black race (black/other) Charlson score (≥4 vs. <4), glomular filtration rate (GFR, continuous), surgery year (continuous), symptom presentation (asymptomatic/local/distant symptoms), and T stage (≥T3 vs. <T3). As Fuhrman grade was not available for non-clear cell histology it was not used in multivariate models.

Separate subgroup analyses of were performed to assess whether the effects of statins varied by type (atorvastatin, Simvastatin, and other) and dose (equivalents of <10mg, 10mg, >10mg atorvastatin.[13] Missing statin types were excluded from the subgroup analysis on type. Additional subgroup analyses compared clear cell with non-clear cell histology and stage (>T2 vs. ≤T2).

We planned a sensitivity analysis to evaluate whether statin use between surgery and follow up is associated with progression and overall mortality. Statin use was entered as a time-dependent covariate into the multivariable models for progression and overall mortality. Date of surgery was considered the statin start date for patients who started statins prior to surgery. Patients starting statins after surgery but before progression contributed person-time to the nonuser group until starting statins, where they contributed person-time to the statin group. Patients who stopped statin use prior to surgery were considered nonusers (n=21). To test whether the result from the sensitivity analysis was different from the main analysis, we used a Chi-squared test for heterogeneity. Survival time was calculated from surgery. Statistical analyses were conducted using Stata 12 (StataCorp, College Station, TX).

Results

Seven hundred and eight (27%) patients were on a statin at surgery. Among nonusers at surgery, 204 (8%) subsequently started statins at a median of 3.9 years after surgery.

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Baseline demographic and clinical characteristics of statin users and nonusers are summarized in Table 1 and statin type and dose distribution in Table 2. Statin users were older (66 vs. 60 years), tended to have worse comorbidities (19% vs. 10% Charlson score≥ 4), worse ASA (57% vs. 33% class 3/4), and were more likely to undergo partial nephrectomy (64% vs. 54%). Statin use was higher among patients treated in recent years. There were no large differences in pathologic features between statin users and nonusers at surgery (Table 3).

On follow up, 247 (9.5%) patients experienced progression, 179 (7%) patients died of RCC, and 316 (12%) patients died of other causes. Median follow up was 3.0 years for patients who did not experience progression or die of other causes. The associations of statin use and other predictors with progression and overall mortality are shown in Table 4. Statin use at surgery was significantly associated with reduced risk of progression (HR 0.67, 95% C.I. 0.47, 0.96, p=0.028) after adjusting for clinical, demographic, and pathologic characteristics. There was no statistically significant difference in overall mortality between statin users and nonusers at surgery in the multivariable model (HR 0.89, 95%CI 0.71, 1.13, p=0.3).

No significant interaction effects were noted, including age (p-interaction=0.8 and p=0.6 for progression and overall mortality respectively) and gender (p-interaction p>0.95 and p=0.2 for progression and overall mortality respectively). In subgroup analyses restricted to statin users at surgery, no significant associations were found between statin dose and progression (>10mg vs. <10mg equivalent of atorvastatin: p=0.15; 10mg vs. <10mg equivalent of atorvastatin: p=0.3) or statin type and progression (atorvastatin vs. simvastatin: p=0.9; atorvastatin vs. other statin types: p=0.6, graph in supplemental materials).

We performed two sensitivity analyses. On multivariable analyses, more recent surgery was associated with higher progression risk (p<0.0001). When surgery year was removed from the model, risk of progression remained lower with statin use at surgery, but the association was no longer statistically significant (HR 0.84, 95%CI 0.60, 1.17, p=0.3). This effect was not explained by more aggressive tumors being operated on more recently, as the proportion ≥T3 was comparable during 1995–2000, 2001–2005, and 2006–2010 (28%, 20% and 24% respectively).

As some patients started statins after surgery (n=204) and stopped during follow up (n=78), the preplanned sensitivity analysis examined the effect of duration of exposure. When statin use was analyzed as a time-dependent covariate, progression risk was lower for statin users but no longer statistically significant (HR 0.77, 95% 0.56, 1.07, p=0.12). The risk of overall mortality was 29% lower in statin users after surgery compared with statin never-users on multivariable analysis (HR 0.71, 95% CI 0.58, 0.88, p=0.002).

As estimates for statin use were not consistent between the main and time-dependent analyses, we tested whether the two analyses were evaluating the same effect. There was no evidence of heterogeneity in the estimates between statin use at surgery and statin use after surgery for either progression or overall mortality (p=0.6 and p=0.17 respectively).

Lastly, we repeated the multivariable analyses stratifying by clear cell (n=1765) vs. non-clear cell (n=843) histology. Results were similar to the overall analyses, though not

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reaching statistical significance due to reduced numbers in the subgroups. Statin use was associated with similar reduced risk of progression in both the clear cell (HR 0.72, p=0.10) and non-clear cell (HR 0.57, p=0.20) subgroups and overall mortality in clear cell (HR 0.90, p=0.50) and non-clear cell (HR 0.91, p=0.70) subgroups. Finally, no difference in the statin-progression or statin-mortality association was noted across stage (>T2 vs. ≤T2; p-interaction p=0.8 and p=0.4, respectively).

Discussion

Currently there are no approved therapies to reduce the probability of progression after surgery for localized RCC. Given the evidence that statins may have antineoplastic properties, we sought to examine the association between statin use and progression and overall mortality after surgery. This study is the first to report this association. We observed statin use was significantly associated with a reduction in the risk of progression, defined as metastases or death from RCC. Statin use was not significantly associated with reduced overall mortality, which was comprised of mostly non-cancer related deaths. When accounting for patients starting statins after surgery, reduction in progression was no longer statistically significant, while reduction in overall mortality became more pronounced.

Unlike in other malignancies, the relationship between statin medications and RCC development and progression is poorly studied. There have only been three studies to directly explore statin use and the risk of developing RCC. The largest, a retrospective case-control study of nearly 500,000 patients observed after adjusting for age, sex, BMI and smoking status, that statin use prior to diagnosis was associated with a 48% reduction in the RCC risk (OR 0.52, 95% CI 0.45–0.60).[10] This risk reduction held across strata of age, BMI and smoking status. A second study combined two U.S. prospective cohorts and totaled over 100,000 patients with a median follow-up of 15 years. In multivariate analyses, statins appeared protective of RCC in women (RR 0.68, 95% CI 0.46–1.00) but not in men (RR 1.17, 95% CI 0.75–1.82).[11] Longer statin use was not associated with reduced risk. Finally, in a study of 177 cases and 708 controls from Taiwan, no significant risk reduction was noted (OR 1.08, 95% CI 0.70–1.67) and no dose or duration effect was observed.[12] Other studies of statin use and cardiovascular outcomes have explored associations with RCC *post hoc* with varied results.[14–17] However, these studies lack power with limited long-term follow-up and numbers of incident RCCs.

To date no study has explored the association between statin use and progression after primary treatment for RCC. However, there is rationale suggesting statins may reduce progression.

A small number of laboratory and animal studies suggest statins may inhibit RCC progression. Woodard et al., administered fluvastatin to two RCC cell lines, 786-0 and CaKi-2.[8] Fluvastatin inhibited growth and induced apoptosis in a dose-dependent manner. Moreover, fluvastatin appeared to directly target the Akt/mTOR pathway, suppressing phosphorylation and thus activation of AkT, reducing downstream mTOR activation. As the mTOR pathway has been implicated in the pathogenesis of RCC and the mTOR inhibitors

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everolimus and temsirolimus have proven benefits in metastatic RCC, the finding that statins inhibit RCC through a similar pathway is relevant.

Bil et al., studied lovastatin with sunitinib or sorafenib in the Renca RCC cell line.[18] They observed lovastatin potentiated the cytotoxic effects of sorafenib, but not sunitinib, and induced cell cycle arrest in the G1 phase.

Finally, Horiguchi et al., observed that fluvastatin, in addition to inhibiting proliferation of Renca cell lines, also inhibited angiogenesis and invasion, two key mechanisms required for progression and metastasis.[9] They validated these findings by xenografting Renca cells into mice and observed fluvastatin inhibited pulmonary metastases.

Statins have been shown to be associated with a reduced risk of prostate cancer progression after radiotherapy,[19] and after surgery;[20] and they have been associated with reduced risk of breast cancer recurrence after primary therapy.[21,22] Recently, a large population-based study of 300,000 Danish cancer patients observed statin users were 15% less likely to die from all cancers (HR 0.85, 95% CI 0.82–0.87). In a supplementary table, they reported statin use was associated with a similar 15% reduction in risk of dying from RCC (2,717 of 124,000 cancer deaths), but this findings did not reach statistical significance (HR 0.85, 95% CI 0.72–1.01). While strengthened by numbers and integrity of exposure and cancer data, this study is limited by lack of information on comorbidities.

We found a statistically significant 33% reduction in progression for statin users at surgery. Considering our sensitivity analysis accounted for the 204 (8%) patients who subsequently started statin use on average nearly 4 years after surgery, it is not surprising the hazard ratio for progression was attenuated. Statin use remained associated with a reduction in progression (23%) but this was no longer statistically significant. These patients may not have had sufficient exposure to statins prior to progression.

In our primary analysis, statin use was associated with an overall survival benefit of 11%, though not statistically significant. This is nearly identical to the overall survival benefit seen in studies of non-cancer patients on statins,[23] and similar to the overall survival benefit observed in the recent Danish study of all cancer patients.[24]

Our finding of a lack of dose- and duration- dependent statin effect does not lend support to a causal association. However, inconsistency in dose-dependent statin antineoplastic effects has been observed in other cancers.[20,25,26] Furthermore, statins are often dosed to optimize lipid response. Thus, taken in cross-section, it is likely the statin doses seen in our cohort produce similar biological effects in cholesterol reduction in each patient and thus may explain the lack of difference in antineoplastic effect.

Our study has limitations. In our cohort, statin users had substantially different baseline clinical and demographic features. They were older, heavier, and had more comorbidities and worse baseline kidney function. Similar findings have been observed in many cohorts when stratified by statin use.[11,20,24,27] Statin users may also differ in health-seeking behaviors. Thus, crude associations between statin use and outcomes may merely reflect the influence of confounding variables. Adjusting for known confounders, as we did, minimizes

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this bias but does not eliminate it as a randomized controlled trial would. Furthermore, as patients are frequently referred to MSKCC for a surgical opinion, information on length of statin use predating initial consultation was rarely available. The association between statin use and reduced progression may be strengthened by pre-surgical statin use not captured in this study.

Conclusions

Our study is the first to directly examine the association between statin use at the time of surgery and progression to metastasis or RCC death. Statin use was associated with a significant reduction in the risk of progression. Although we observed no significant relationship between dose and duration of statin use and progression and our sensitivity analysis accounting for statin use after surgery saw statin use trend towards protective but no longer statistically significant, our findings merit further exploration. The association between statins and outcome should be reported for other RCC surgical cohorts and in secondary analyses of the many trials of VEGF- and mTOR-pathway inhibitors. If similar results are observed, a randomized controlled trial of statin initiation prior to surgery for localized RCC should be considered.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Baseline characteristics of statin users vs. nonusers at surgery. All values are median (interquartile range) or frequency (proportion).

	No statin use at surgery (N=1900)	Statin use at surgery (N=708)	P-value
Age at Surgery	59 (50, 68)	66 (59, 72)	<0.001
Male	1209 (64%)	482 (68%)	0.034
Race			
White	1702 (90%)	644 (91%)	
Black	110 (6%)	32 (5%)	0.6
Asian	57 (3%)	23 (3%)	
Other/Unknown	31 (1%)	9 (1%)	
Married	1377 (72%)	514 (73%)	0.9
Year of surgery			
1995–2000	533 (28%)	62 (9%)	
2001–2005	618 (33%)	245 (35%)	<0.001
2006–2010	749 (39%)	401 (57%)	
Body mass index (kg/m^2)			
≤25	448 (27%)	95 (16%)	
26–30	608 (37%)	240 (41%)	<0.001
31–35	310 (19%)	153 (26%)	
≥36	266 (16%)	101 (17%)	
Charlson score category			
2–3	1716 (90%)	577 (81%)	<0.001
≥4	184 (10%)	131 (19%)	
Presentation			
Asymptomatic	1407 (76%)	542 (80%)	
Local	381 (21%)	115 (17%)	0.12
Systemic	61 (3%)	23 (3%)	
Preoperative GFR (mL/min/1.73 m2)	69 (59, 80)	64 (53, 76)	<0.001
Left side	940 (49%)	347 (49%)	0.8
Clinical stage			
T1a	717 (61%)	202 (60%)	
T1b	139 (12%)	37 (11%)	0.7
T2	130 (11%)	34 (10%)	
T3	188 (16%)	63 (19%)	
T4	7 (1%)	3 (1%)	

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	No statin use at surgery (N=1900)	Statin use at surgery (N=708)	P-value
ASA			
1	133 (7%)	8 (1%)	
2	1124 (60%)	297 (42%)	<0.001
3	593 (32%)	386 (55%)	
4	12 (1%)	11 (2%)	
Length of stay (days)	4 (3, 6)	4 (3, 5)	<0.001
Minimally invasive approach	226 (12%)	117 (17%)	0.002
Partial nephrectomy	1028 (54%)	454 (64%)	<0.001

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Table 2

Proportions of statin medication and dose equivalency for statin users at surgery

	N=708
Statin medication	
Atorvastatin	326 (46%)
Fluvastatin	5 (1%)
Lovastatin	15 (2%)
Pravastatin	53 (7%)
Rosuvastatin	66 (9%)
Simvastatin	236 (33%)
Missing statin type	7 (1%)
Statin dose equivalent	
<Atorvastatin 10mg	78 (11%)
= Atorvastatin 10mg	248 (35%)
> Atorvastatin 10mg	315 (44%)
Missing dose	67 (9%)

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Table 3

Pathological features at nephrectomy of statin users and non users at surgery. All values are median (interquartile range) or frequency (proportion).

	No statin use at surgery (N=1900)	Statin use at surgery (N=708)
Pathological stage		
T1a	926 (49%)	371 (53%)
T1b	385 (20%)	129 (18%)
T2	137 (7%)	41 (6%)
T3	441 (23%)	157 (22%)
T4	7 (0%)	7 (1%)
Maximum diameter (cm)	4.0 (2.5, 6.0)	3.5 (2.5, 5.5)
Grade		
Low	580 (31%)	257 (36%)
High	369 (19%)	195 (28%)
Missing	951 (50%)	256 (36%)
Lymph node involvement		
No	530 (28%)	166 (23%)
Yes	36 (2%)	12 (2%)
Missing or not done	1334 (70%)	530 (75%)
Multifocal disease	112 (6%)	55 (8%)
Surgical margin status		
Negative	1566 (82%)	648 (92%)
Positive	96 (5%)	29 (4%)
Missing	238 (13%)	31 (4%)
Postoperative GFR (mL/min/1.73 m2)	56 (46, 68)	52 (41, 63)
Histology		
Clear Cell	1293 (68%)	472 (67%)
Papillary	257 (14%)	116 (16%)
Chromophobe	230 (12%)	68 (10%)
Unclassified /Other	120 (6%)	52 (7%)

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Table 4

Multivariable analysis to evaluate predictors of progression and overall mortality among statin users and non users at surgery

	Progression			Overall Mortality		
Predictor	**Hazard ratio**	**95% CI**	**P-value**	**Hazard ratio**	**95% CI**	**P-value**
Statin use at surgery	0.67	0.47, 0.96	0.028	0.89	0.71, 1.13	0.3
Age per 10 years	1.02	0.92, 1.13	0.7	1.66	1.52, 1.82	<0.0001
Male	1.29	0.95, 1.75	0.10	1.04	0.85, 1.27	0.7
Black race	0.76	0.40, 1.45	0.4	1.27	0.85, 1.89	0.2
Partial nephrectomy	0.25	0.16, 0.37	<0.0001	0.65	0.51, 0.81	0.0002
Charlson co-morbidity score ≥4 vs. <4	2.22	1.59, 3.08	<0.0001	1.33	1.05, 1.68	0.019
Pathological stage ≥T3 vs. <T3	2.42	1.82, 3.23	<0.0001	1.64	1.35, 2.00	<0.0001
Pre-operative GFR per 10 units	0.99	0.90, 1.09	0.9	0.92	0.87, 0.98	0.010
Local symptom vs. incidental	2.09	1.56, 2.80	<0.0001	1.09	0.87, 1.36	0.4
Systemic symptom vs. incidental	3.77	2.39, 5.93	<0.0001	3.47	2.49, 4.83	<0.0001
Year of surgery	1.08	1.04, 1.13	<0.0001	1.11	1.07, 1.15	<0.0001