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## Platinum Priority – Kidney Cancer

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# Long-term Use of Statins and Risk of Renal Cell Carcinoma: A Population-based Case–Control Study

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### Abstract

**Background:** Use of statins has been suggested to protect against renal cell carcinoma (RCC); however, studies have typically been underpowered, and the results are conflicting.

**Objective:** To determine whether the use of statins is associated with a reduced risk of RCC using high-quality registry data.

**Design, setting, and participants:** We conducted a nationwide case–control study based on all histologically verified cases of RCC in Denmark between 2002 and 2012 ( $n = 4606$ ) matched 1:10 to cancer-free controls. Data on drug use, comorbidity, and educational level were obtained from Danish nationwide prescription, patient, and demographic registries.

**Outcome measurements and statistical analysis:** Odds ratios (ORs) and 95% confidence intervals (CIs) for RCC associated with long-term use ( $\geq 5$  yr) of statins were estimated using conditional logistic regression, adjusting for potential confounders.

**Results and limitations:** The adjusted OR for RCC associated with long-term use of statins was 1.06 (95% CI, 0.91–1.23). Analyses stratified by duration of statin use, type of statin, and patient characteristics all yielded ORs close to unity, except for a slightly increased OR for RCC associated with long-term statin use among women (OR: 1.25; 95% CI, 0.96–1.62). The main limitation of our study was lack of information on lifestyle factors, notably obesity, which may have biased the risk estimates upward.

**Conclusions:** Our study does not support an important chemopreventive effect of long-term statin use against RCC. The marginally increased and statistically insignificant risk estimates can readily be interpreted as a null finding, considering the lack of control for obesity and other lifestyle risk factors.

**Patient summary:** Previous studies have shown that the use of cholesterol-lowering drugs (statins) may protect against renal cancer. In a large study including all Danish renal cancers during an 11-yr period, we found no evidence of such an effect.

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## 1. Introduction

Although laboratory studies have consistently demonstrated the antineoplastic effects of statins against several cancer types [1–3], epidemiological studies are conflicting regarding the association between statin use and cancer risk [3–6]. Studies that have reported results for the association between statin use and kidney cancer have also produced equivocal results [7–13]. A cohort study of US veterans reported a 48% reduction in the risk of renal cell carcinoma (RCC) associated with statin use [10], and two small population-based cohort studies found a similar inverse association [11]. In contrast to these studies, other epidemiological studies have found no apparent association between statin use and the risk of RCC or kidney cancer overall [7–9,12], and one study reported an increased risk of kidney and other urologic cancers associated with statin use [13].

The Danish health system offers unique opportunities to study associations between drug use and cancer risk in large population-based cohorts. Using a nationwide population-based case–control design, we aimed to evaluate the hypothesis that statin use is associated with a reduced RCC risk.

## 2. Material and methods

The study was conducted as a nationwide case–control study. We compared the use of statins among individuals diagnosed with RCC (cases) with use among cancer-free individuals (controls) to estimate the odds ratio (OR) for RCC associated with long-term use of statins defined as cumulative exposure of a minimum of 5 yr.

### 2.1. Data sources

We used data from five Danish nationwide registries: the Danish Cancer Registry [14], the National Prescription Registry [15], the National Patient Register [16], registers in Statistics Denmark with information on level of education [17], and the Civil Registration System [18]. Supplement 1 describes the data sources in detail.

Virtually all medical care in Denmark is furnished by the national health authorities, allowing true population-based register-linkage studies covering all inhabitants of Denmark. Data were linked by use of the personal identification number, a unique identifier assigned to all Danish residents since 1968 [18]. All linkages were performed within Statistics Denmark, a governmental institution that collects and processes information for a variety of statistical and scientific purposes.

### 2.2. Cases and controls

From the Danish Cancer Registry, we identified all individuals in Denmark with a first-time diagnosis of invasive parenchymal RCC (ie, disregarding cancers of the pelvis and in situ cancers) between January 1, 2002, and December 31, 2012. The date of cancer diagnosis was defined as the index date. To ensure the validity of our case material, we restricted cases to histologically verified cases. Exclusion criteria were age outside the range of 18–85 yr at the index date and residency outside Denmark within 10 yr prior to the index date, thus ensuring at least 10 yr of follow-up for all study subjects and a minimum of 7 yr of prescription coverage (see Supplement 1). We further excluded individuals with a history of cancer (except nonmelanoma skin cancer)

or conditions disposing to RCC including von Hippel-Lindau syndrome (International Classification of Diseases [ICD]-8: 75982; ICD-10: Q85.8–9), cystic kidney disease (ICD-8: 59324; ICD-10: Q61), and tuberous sclerosis (ICD-8: 31032, 31132, 31232, 31332, 31432, 31532, 75969; ICD-10: Q851).

Controls were selected using risk set sampling. For each case, we selected 10 controls among all Danish residents of the same gender and birth year and applied the same selection criteria as for cases. Controls were assigned an index date identical to that of the corresponding case.

Subjects were eligible for sampling as controls before they became cases. The calculated ORs are unbiased estimates of the incidence rate ratios that would have emerged from a cohort study in the source population [19].

### 2.3. Exposure definition

Our primary exposure was the use of statins. “Ever use” of statins was defined as having filled two or more prescriptions (Anatomical Therapeutic Chemical [ATC] code C10AA) of any statin prior to the index date. Long-term use of statins was defined as  $\geq 5$  yr of cumulative use prior to the index date. We performed extensive sensitivity analyses of the exposure definition. The duration of each prescription, required for the estimation of cumulative exposure duration, is not recorded in the National Prescription Registry. To overcome this limitation, we assumed a daily intake of one tablet while adding 25% additional days to the duration to allow for minor noncompliance and irregular refill patterns. In all exposure calculations, we disregarded prescriptions redeemed within 1 yr prior to the index date. This was done to reduce the possibility of reverse causation [20,21] and from the rationale that such recent exposure is unlikely to be associated with cancer development.

### 2.4. Main analysis

The analysis followed a conventional matched case–control approach. In the main analysis, we estimated ORs for RCC associated with long-term use of statins. In all analyses, use of statins was compared with nonuse (fewer than two prescriptions) of statins using conditional logistic regression.

Using data from the prescription, patient, and demographic registries, and disregarding the period 1 yr prior to the index date, we incorporated a number of potential confounders in the analyses: (1) use of drugs known or suspected to modify renal function or risk of RCC including low-dose aspirin and nonaspirin nonsteroidal anti-inflammatory drugs, paracetamol, thiazides,  $\beta$ -blockers, vascular calcium channel blockers, inhibitors of the renin-angiotensin system, and loop diuretics; (2) prior diagnoses of diseases known or suspected to modify renal function or risk of renal or other cancers including hypertension, type 1 or type 2 diabetes, chronic obstructive pulmonary disease, alcohol-related disease, and moderate to severe renal disease; and (3) highest achieved education (as a crude measure of socioeconomic status). Supplementary Table 1 presents the details of the potential confounders including codes.

### 2.5. Sensitivity and supplementary analyses

We performed a number of predefined subanalyses and sensitivity analyses. First, as an explorative analysis of a potential dose–response effect, we performed analyses stratified according to cumulative use of statins. This was done for statins overall and separately for hydrophilic, lipophilic, and individual statin drugs (see Supplement 2 for definitions). Second, we examined associations for RCC with statin use within subgroups defined by gender, age, or histories of renal disease, diabetes, or hypertension. Third, we stratified the analyses by clinical stage, defined as localized or nonlocalized disease. Fourth, we changed the 1-yr

lag time to zero or 2 yr, respectively. Finally, we used the “rule-out” approach, described by Schneeweiss [22], to assess the extent to which any positive associations might be explained by unmeasured confounding by overweight.

## 2.6. Other

All analyses were performed using Stata v.13.0 (StataCorp, College Station, TX, USA). The study was approved by the Danish Data Protection Agency. According to Danish law, studies based solely on register data do not require approval from an ethics review board [23].

## 3. Results

We identified 5631 incident RCCs between January 2002 and December 2012. After exclusions, the study population consisted of 4606 cancer cases (Fig. 1) who were matched to 46 060 controls.

Among cases, 24.0% were ever-users of statins and 6.7% were long-term users (Table 1). The corresponding prevalences among controls were 19.1% and 4.9%, respectively. This yielded an age- and gender-adjusted OR for RCC associated with ever use of statins of 1.38 (95% confidence interval [CI], 1.28–1.49) and for long-term use of 1.48 (95% CI, 1.29–1.69). However, after adjustment for potential confounders, the ORs declined to 1.06 (95% CI, 0.97–1.16) for ever use and 1.06 (95% CI, 0.91–1.23) for long-term use (Table 2).

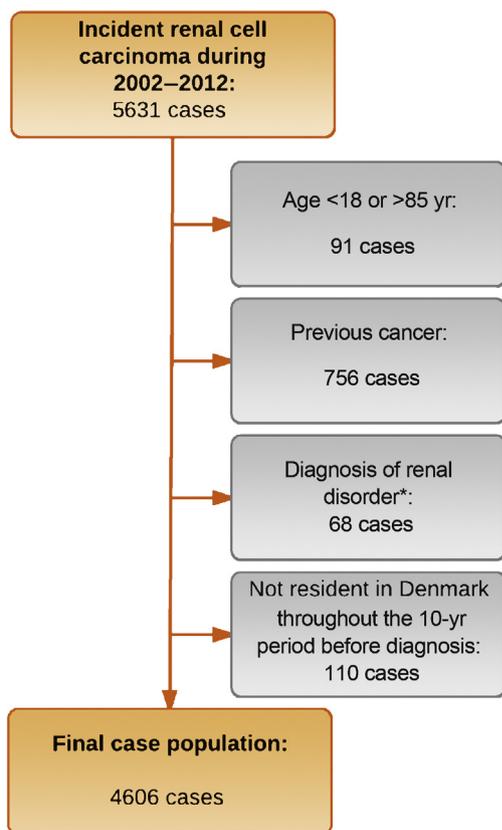


Fig. 1 – Flowchart of the selection of cases.

\* Von Hippel-Lindau syndrome, cystic kidney disease, and tuberous sclerosis.

Table 1 – Characteristics of renal cell carcinoma cases and their matched controls

	All cases (n = 4606)	All controls (n = 46 060)
Age, median, yr (IQR)	64 (57–72)	64 (57–72)
Male sex (%)	3052 (66.3)	30 520 (66.3)
Use of statins prior to index date (%)		
Nonuse	3501 (76.0)	37 241 (80.9)
Ever use	1105 (24.0)	8819 (19.1)
Long-term use (≥5 yr)	307 (6.7)	2275 (4.9)
Drugs (%)		
Nonaspirin NSAID	2661 (57.8)	23 737 (51.5)
Aspirin	1205 (26.2)	9638 (20.9)
Paracetamol	892 (19.4)	7128 (15.5)
Loop diuretics	619 (13.4)	4194 (9.1)
Thiazides	1212 (26.3)	8808 (19.1)
β-Blockers	1216 (26.4)	9086 (19.7)
Vascular calcium channel blockers	1075 (23.3)	7083 (15.4)
Inhibitors of RAS	1641 (35.6)	11 162 (24.2)
Medical history (%)		
Hypertension	809 (17.6)	5212 (11.3)
Diabetes type 1	131 (2.8)	843 (1.8)
Diabetes type 2	503 (10.9)	3536 (7.7)
COPD	341 (7.4)	3015 (6.5)
Alcohol-related disease	364 (7.9)	3276 (7.1)
Moderate/severe renal disease	116 (2.5)	456 (1.0)
Highest achieved education, yr (%)		
Short (7–10)	1811 (39.3)	16 820 (36.5)
Medium (11–13)	1808 (39.3)	17 975 (39.0)
Long (>13)	758 (16.5)	9336 (20.3)

COPD = chronic obstructive pulmonary disease; IQR = interquartile range; NSAID = nonsteroidal anti-inflammatory drug; RAS = renin-angiotensin system.

The pronounced effect of the confounder adjustment is further illustrated in Supplementary Table 2. All the included potential confounders contributed to attenuation of the association between statin use and RCC risk, notably diagnoses of hypertension and inhibitors of the renin-angiotensin system.

In analyses stratified by duration of statin use, all ORs were close to unity (Table 2). Stratification by lipophilic or hydrophilic statins (Supplementary Table 3) and by individual statin drugs (Supplementary Table 4) did not alter the associations materially. Analyses within predefined subgroups of gender, age, comorbidity, or clinical stage revealed a slightly but statistically nonsignificant increased OR for RCC with long-term statin use among women (OR: 1.25; 95% CI, 0.96–1.62), whereas no risk variation was found according to the other subgroups (Table 3).

In the sensitivity analysis including statin exposure within 1 yr prior to the index date, the ORs increased slightly. Overall, the adjusted OR for long-term statin use increased to 1.14 (95% CI, 0.99–1.31), driven by an OR for the last year preceding the index date of 1.22 (95% CI, 1.07–1.40). Increasing the lag period to 2 yr did not influence the estimates.

We also ascertained whether the point estimate of 1.25 among women could be explained by residual confounding from being overweight. The input for this analysis was an estimated prevalence of overweight of 36.8% among women [24] and an exposure prevalence of 4%

**Table 2 – Association between exposure to statins and risk of renal cell carcinoma, specified by exposure pattern**

Exposure group	Cases, <i>n</i>	Controls, <i>n</i>	Adjusted OR <sup>a</sup>	Adjusted OR <sup>b</sup>
Nonuse	3501	37 241	1.00 (ref.)	1.00 (ref.)
Ever use	1105	8819	1.38 (1.28–1.49)	1.06 (0.97–1.16)
Long-term use (≥5 yr)	307	2275	1.48 (1.29–1.69)	1.06 (0.91–1.23)
Cumulative duration of use				
<1 yr	238	2128	1.20 (1.04–1.38)	1.00 (0.86–1.15)
1–4.99 yr	560	4416	1.42 (1.29–1.57)	1.09 (0.97–1.22)
5–9.99 yr	250	1879	1.46 (1.26–1.68)	1.03 (0.88–1.21)
≥10 yr	57	396	1.55 (1.15–2.08)	1.11 (0.81–1.51)

OR = odds ratio.

<sup>a</sup> Adjusted for age and sex (by design; risk-set matching).<sup>b</sup> Adjusted for (a) use of low-dose aspirin and nonaspirin nonsteroidal anti-inflammatory drugs, paracetamol, thiazides, β-blockers, vascular calcium channel blockers, inhibitors of the renin-angiotensin system, and loop diuretics; (b) prior diagnoses of hypertension, type 1 or type 2 diabetes, chronic obstructive pulmonary disease, alcohol-related disease, and moderate to severe renal disease; and (c) highest achieved education.**Table 3 – Associations between long-term exposure to statins (≥5 yr) and risk of renal cell carcinoma, specified by patient subgroups or cancer stage**

Subgroup	Cases, exposed/ unexposed, <i>n/n</i>	Controls, exposed/ unexposed, <i>n/n</i>	Adjusted OR <sup>a</sup>	Adjusted OR <sup>b</sup>
All	307/3501	2275/37 241	1.48 (1.29–1.69)	1.06 (0.91–1.23)
Male	200/2312	1602/24 530	1.32 (1.12–1.56)	0.96 (0.80–1.16)
Female	107/1189	673/12 711	1.88 (1.49–2.37)	1.25 (0.96–1.62)
Age <50 yr	–/461	17/4751	–	–
Age 50–69 yr	143/2004	1018/21 593	1.55 (1.28–1.88)	0.99 (0.79–1.23)
Age ≥70 yr	161/1036	1240/10 897	1.40 (1.16–1.70)	1.13 (0.91–1.40)
No history of renal disease	289/3431	2212/36 978	1.46 (1.27–1.67)	1.08 (0.93–1.26)
No history of hypertension	162/3110	1432/34 732	1.32 (1.10–1.57)	1.06 (0.87–1.28)
No history of diabetes	207/3268	1734/35 291	1.33 (1.13–1.56)	0.92 (0.77–1.10)
Stage				
Localised	195/2027	1361/21 966	1.61 (1.36–1.91)	1.05 (0.86–1.27)
Nonlocalised	64/1108	583/11 345	1.12 (0.85–1.48)	0.98 (0.72–1.34)
Unknown	48/366	331/3930	1.68 (1.19–2.37)	1.22 (0.82–1.83)

OR = odds ratio.

<sup>a</sup> Adjusted for age and sex (by design).<sup>b</sup> Adjusted for (a) use of low-dose aspirin and nonaspirin nonsteroidal anti-inflammatory drugs, paracetamol, thiazides, β-blockers, vascular calcium channel blockers, inhibitors of the renin-angiotensin system, and loop diuretics; (b) prior diagnoses of hypertension, type 1 or type 2 diabetes, chronic obstructive pulmonary disease, alcohol-related disease, and moderate to severe renal disease; and (c) highest achieved education.

among female controls (Table 3). A similar analysis was performed, assuming the same exposure prevalence and a smoker prevalence of 30.6% for women [25]. Both analyses (Supplementary Fig. 1) showed that with ORs <2.0 for the association between being overweight/smoking and RCC risk, there would have to be an extremely strong association between overweight/smoking and statin use to fully account for an apparent OR of 1.25 if the true value was 1.00.

Finally, we performed a number of post hoc analyses. To further evaluate the observed risk variation by gender, we stratified the analyses of duration of statin use by gender (Supplementary Table 5). In addition, we repeated the analysis for women excluding users of any hormone supplement prior to the index date, whereby the OR increased from 1.25 to 1.42 (95% CI, 0.93–2.16). To further investigate the influence of timing of statin use on RCC risk, we restricted the study population to subjects with at least 10 yr of exposure data (ie, with index dates between 2005 and 2012; 77% of cases; *n* = 3526) and disregarded exposure within the last 5 yr prior to the index date. The overall OR of this analysis (1.03; 95% CI, 0.82–1.31) was

close to that of the main analysis (1.06). Lastly, to evaluate the performance of our algorithm for cumulative exposure of statins, we omitted the 25% added to the expected duration of prescriptions for statins (see sect. 2). This analysis also returned results similar to those of the main analysis (data not shown).

#### 4. Discussion

In this nationwide study including all Danish RCC cases from 2002 to 2012, we found no evidence of a chemopreventive effect of long-term statin use on RCC. Except for a slightly elevated OR for RCC among female statin users, the risk estimates were all close to unity, and the results were robust within a supplementary analysis of subgroups and in dose–response analyses.

Our results are consistent with most of the studies of statin use and risk of kidney cancer [7–9,12,26]. Three studies reported a substantial reduction in risk of RCC or kidney cancer overall with statin use [4,10,11]; however, these results were prone to methodological shortcomings.

In the case–control study of US veterans by Khurana et al [10], controls were drawn from among frequent users of the Veterans Affairs system who may have been more likely to be prescribed statins than the kidney cancer cases included in the study, thus introducing selection bias. In the cohort study by Liu et al [11], the inverse association between statin use and RCC risk was confined to a subgroup of the study population (ie, women without hypertension), and, finally, the statistical precision and drug exposure period were limited in the case–control study by Graaf et al [4] preventing analyses according to duration of statin use for cancer subsites. A 2014 meta-analysis, including data from both observational studies and randomized trials, reported a pooled risk ratio for the association between statin use and kidney cancer close to unity (0.92; 95% CI, 0.71–1.19), with no risk variation according to duration of statin use [26].

The main limitation of our study is lack of individual anthropometric data. Confounding from being overweight would increase the observed OR. Because we could not test directly the association between being overweight and RCC risk, we used a sensitivity analysis based on published reports of obesity and RCC risk to determine how large an association between being overweight and statin use would have to exist to account for the 1.25 OR point estimate observed among women (Supplementary Fig. 1). Our analyses showed that it is highly unlikely that the OR of 1.25 was entirely explained by residual confounding by obesity or smoking, if the true OR was 1.00. If we assume an OR between being overweight and RCC of 1.34 for women, as reported in one meta-analysis [27] and a risk ratio between smoking and RCC of up to 1.58 reported in another meta-analysis [28], then it becomes virtually impossible that obesity and smoking are the sole explanations because this would require that statins were almost exclusively prescribed to obese or smoking patients. To our knowledge, smoking and obesity have never been included in Danish guidelines as indications for prescribing statins, except if these risk factors were believed to have caused diabetes or an atherosclerotic event. Both of these conditions were well captured in our analysis. However, the CI of our estimate included the null value, and thus we cannot rule out that our finding is attributable to random error. Importantly, in our analysis, confounding from lifestyle factors appeared less important for the association between statin use and risk of RCC than factors such as hypertension and use of inhibitors of the renin-angiotensin system (Supplementary Table 2).

Another limitation of our study was that we were not able to categorize the RCC cases into histologic subgroups (eg, clear cell carcinomas vs non-clear cell carcinomas). Therefore, we cannot entirely exclude an association between statin use and rare subtypes of RCC. Lastly, the homogeneous, primarily white, Danish population may not be representative of all users of statins.

The main strengths of our study were the large sample size and the nationwide approach. In Denmark, we are uniquely positioned to perform a population-based study with almost complete population coverage because almost

all health care service in the country is administered by the public health system. The RCC cases were identified from the Danish Cancer Registry, which has accurate and virtually complete registration of incident cancer in Denmark [14,29], and the additional restriction to histologically verified cases further enhanced the case validity. The use of the Danish National Prescription Registry also ensured complete and high-quality assessment of drug use [15], with up to 18 yr of drug exposure history.

## 5. Conclusions

Our large population-based study, including high-quality register data and adjusting for important confounders, did not support an important chemopreventive effect of long-term statin use against RCC. We interpret the marginally increased and statistically insignificant ORs for RCC with long-term statin use as a null finding considering the lack of control for obesity and other lifestyle risk factors.

**Author contributions:** Anton Pottegård had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Lund, Pottegård, Hallas.

**Acquisition of data:** Pottegård, Hallas.

**Analysis and interpretation of data:** Pottegård (analysis), Clark, Friis, Hallas, Lars Lund (interpretation).

**Drafting of the manuscript:** Pottegård, Clark, Friis, Hallas, Lund.

**Critical revision of the manuscript for important intellectual content:** Pottegård, Clark, Friis, Hallas, Lund.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.eururo.2015.10.020>.

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