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 (≥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 ≥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 noneuse (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, β-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