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STATIN USE AND THE RISK OF RENAL CELL CARCINOMA IN 2 PROSPECTIVE US COHORTS

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Abstract

Background—Statins are widely used cholesterol-lowering agents that may have potential anti-tumor effect. Epidemiological studies on statin use and renal cell carcinoma (RCC) risk have been inconsistent.

Methods—We investigated the association between statin use and RCC risk in the Nurses' Health Study and Health Professionals Follow-up Study. A total of 80,782 women and 37,869 men were followed for 14 and 16 years respectively. Regular statin use was assessed at baseline and updated biennially during follow-up. RCC diagnosis was confirmed by medical record review.

Results—We identified 277 incident RCC cases (164 women and 113 men). Compared with no current use, the multivariate relative risks for current statin use were 0.68 (95% CI: 0.46, 1.00) in women and 1.17 (95% CI, 0.75, 1.82) in men. The results for ever versus never users of statins were similar. We found no dose-response relation with duration of statin use and RCC risk. On subgroup analyses, statin use was associated with a reduced RCC risk among women with no history of hypertension.

Conclusions—Statin use may be associated with a lower risk of RCC in women, although these results need to be further investigated.

Keywords

carcinoma; renal cell; neoplasms; statin; prospective studies

INTRODUCTION

The statins are currently the most commonly prescribed cholesterol-lowering agents that act by inhibiting the enzyme 3-hydroxy 3-methylglutaryl CoA (HMG CoA) reductase. In addition, statins are also widely used in both primary and secondary prevention of cardiovascular diseases [1–3]. Recently, increasing evidences suggest that statins may have potential anti-tumor effects [4, 5] through inducing apoptosis [6], inhibiting angiogenesis, and suppressing tumor metastasis [4, 5].

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Previous epidemiological studies of statin use and the risk of kidney cancer are limited, largely retrospective in nature, and have had conflicting results. While a lower risk of kidney cancer was found in 2 nested case-control studies [7, 8], an increased risk in men was found in a cohort study [9]. However other studies [10–13] found no associations. A recent meta-analysis including some of these studies reported a non-significant inverse association [14]. Few prospective studies exist in the general populations. Therefore, we conducted a prospective analysis in the Nurses' Health Study (NHS) and Health Professionals Follow-up Study (HPFS) to evaluate the influence of statin use on the risk of renal cell carcinoma (RCC), the most common type of kidney cancer [15].

METHODS

Study population

The NHS is a prospective cohort of 121,700 registered nurses who were between the ages of 30 and 55 years and living in 11 states in the United States when they completed an initial questionnaire on their medical history and life-style factors in 1976. The HPFS is a prospective cohort study of 51,529 US male dentists, optometrists, osteopath physicians, podiatrists, pharmacists, and veterinarians, aged 40–75 years at entry, who responded to a baseline questionnaire in 1986. These cohorts are described in details elsewhere [16, 17]. Every 2 years, information was updated on newly diagnosed diseases and other life-style factors. The follow-up rates are nearly 90% in both cohorts. The institutional review boards of the Brigham and Women's Hospital and the Harvard School of Public Health approved the study.

Case ascertainment

We obtained self-reported information on the occurrence of kidney cancer on biennial questionnaires, and asked participants (or next of kin, for those who had died) who reported the diagnosis of kidney cancer for permission to access medical records in the cohorts. Deaths occurring in the cohort were documented by family members in response to the follow-up questionnaires; the National Death Index [18] was searched for those who did not respond. We estimated that more than 98% of deaths were ascertained through these sources, from prior experience [18]. Physicians blinded to exposure status reviewed medical records to confirm RCC diagnosis and to identify histological subtypes. We included only those participants with a diagnosis of RCC identity (International Classification of Diseases for Oncology, 2nd Edition [19], code C64.9 or International Classification of Diseases, 9th Revision, Clinical Modification [20], code 189.0) including clear cell, papillary, chromophobe, and collecting duct RCC, and RCC not otherwise classified, based on the classification developed at a World Health Organization workshop [21]. Transitional cell cancers of the renal pelvis were excluded.

Assessment of exposures

In 1994 (NHS) and 1990 (HPFS) and biennially thereafter, participants were asked whether they regularly (≥2 times per week) used any cholesterol-lowering drugs. Since 2000, participants were asked to report separately whether they regularly used statin drugs or other cholesterol-lowering drugs. In 2000, statin users were also asked to further specify their duration of use in 2-year categories with duration dating back to 1994 (NHS) and 1990 (HPFS), respectively. Statins were first sold in the U.S. in 1987, and soon afterwards became the most popular cholesterol-lowering drugs. Therefore, statins probably constituted the majority of the cholesterol-lowering drugs consumed in our cohorts. Indeed, responses to the 2000 questionnaires indicated that approximately 93% of the cholesterol-lowering drugs used in the NHS and 91% in the HPFS were statins. In the analysis, we defined use of statins based on the information on duration of statin use collected in 2000 as well as information

on use of any cholesterol-lowering medications for the period prior to 2000 and information on statin use from 2000. No information was available on the brand, type, or dose of drugs used.

In both cohorts, participants who reported regular use of statins on a questionnaire were considered as current users for the subsequent 2-year follow-up period. Current non-users of statins during any given follow-up period were those who did not report use on the current questionnaire. We also evaluated never vs. ever users. Never users were defined as individuals who never had used statins during follow-up. Ever users included current and past users during follow-up. In order to provide the best estimate of average long-term use of statins, we also calculated cumulative duration of statin use among ever users by summing over the number of years of use based on response to all available questionnaires [22]. Duration of statin use was evaluated as a categorical variable with cutpoint of 4 years, a value close to the median duration of statin use among statin users in both cohorts. For participants who missed a follow-up questionnaire, drug use information was carried forward one cycle from the previous follow-up cycle.

Assessment of other covariates

In both cohorts, we collected data on the demographics and other risk factors for RCC at baseline and have updated most of these factors every 2 years. Age in months was calculated from date of birth to each questionnaire's return date. Body mass index (BMI) was calculated using height in 1976 and current weight updated every 2 years. Other known or potential risk factors for RCC including smoking, history of hypertension, history of diabetes[23], regular use of nonsteroidal anti-inflammatory drugs (NSAIDs), and physical activity were collected at baseline and updated biennially. Pack-years of smoking were calculated by multiplying the duration and dose of smoking. One pack-year of smoking is equivalent to having smoked one pack per day for one year. Dietary intake including alcohol[24], fruits, and vegetables[25] was assessed at baseline and updated every 4 years thereafter. To generate the physical activity score, we summed activity-specific metabolic equivalent (MET)-hours/week for reported activities, using MET values based on a compendium of activities. One MET-hour is the metabolic equivalent of sitting at rest for 1 hour. Parity[26], defined as number of childbirths, that they had experienced, was queried from 1976 through 1984, when few additional births were reported in the NHS. These covariates were adjusted for as time-varying variables.

Data analysis

At baseline, we excluded participants with a diagnosis of cancer beside nonmelonoma skin cancer and those who did not return the questionnaire containing question on use of cholesterol-lowering medications. After these exclusions, 80,782 women and 37,869 men remained eligible for the analysis.

We calculated person-years from baseline questionnaire return date (1994 in the NHS; 1990 in the HPFS) until the date of RCC diagnosis, date of death, or the end of follow-up (June 2008 for NHS and January 2006 for HPFS), whichever came first. The incidence rates of RCC according to regular use of statins were calculated by dividing the number of incident cases by the total person-years in that category. We used Cox proportional hazards models [27] to estimate relative risks (RRs) and 95% confidence intervals (CIs) after adjusting for other risk factors of RCC. To control as finely as possible for confounding by age, calendar time, and any possible two-way interactions between these two time scales, we stratified the analysis jointly by age in months at start of follow-up and calendar year of the current questionnaire cycle. In the multivariate-adjusted analyses, we additionally controlled for smoking, current BMI (kg/m^2), history of hypertension, history of diabetes, duration of

non-aspirin NSAIDs use, physical activity, and intake of fruit, vegetable, and alcohol in both cohorts and parity in the NHS. The percentage of missing data for the covariates was low in our cohorts. The variable with the highest percentage of missing data was smoking in the HPFS (6.1%) and fruit/vegetable intake in the NHS (15.7%) at baseline. We have created separate missing value category for the covariates with missing values. Analyses were performed using the SAS statistical package, version 9.1 (SAS Institute, Cary, NC). All *P* values were calculated based on 2-sided tests and were considered statistically significant at $P<.05$.

RESULTS

During the 14 years follow-up among 80,782 woman (933,361 person-years) and 16 years among 37,869 men (455,910 person-years), we documented a total of 277 RCC cases (164 women and 113 men) with information on statin use. The prevalence of statin use climbed gradually from 4% in 1994 to 39% in 2006 in the NHS and from 4% 1990 to 38% in 2004 in the HPFS.

As shown in Table 1, statin users tended to be older, to have a higher BMI, to exercise less, and to be a past smokers. Compared with nonusers, regular users of statin were more likely to have comorbidities such as hypertension and diabetes, and to use non-aspirin NSAIDs.

Overall, current use of statins was not associated with the risk of RCC in both women and men in age-adjusted analysis (Table 2). Among the covariates we considered in multivariate models, history of hypertension had the strongest impact on the RRs in both cohorts. Thus, the results adjusting for age and hypertension are presented separately. Adjustment of hypertension had a similar impact of reducing RRs in both cohorts. Additional adjustment for other covariates further reduced the RRs. The RR for women became marginally statistically significant (RR=0.68, 95% CI=0.46–1.00).

We also evaluated never vs. ever use of statins during follow-up as well as duration of use (<4 years vs. ≥4 years) among ever users (Table 3). There was no statistically significant association between ever users of statins and the risk of RCC in age-adjusted analysis in both women and men. We found similar magnitude and direction of confounding by hypertension as the analysis evaluating current usage of statins; the RRs were reduced after we adjusted for hypertension in the cohorts. When we adjusted for multiple risk factors for RCC, the RRs in both cohorts were further reduced. However, none of the RRs were statistically significant. Duration of statin use was not associated with RCC risk also.

We examined baseline statins use without updating the evolving exposure status during follow-up and found no association between statin use and RCC incidence in both cohorts (data not shown). When we excluded RCC cases from the first 2 years of follow-up (n=24 in the NHS and 12 in the HPFS), the results did not materially change (data not shown).

Because history of hypertension was important confounder of the association, we stratified the association between current use of statins and RCC risk by history of hypertension (Table 4). Due to strong positive correlation between history of hypertension and statin use, there were much smaller numbers of cases among those with no history of hypertension. Among those with no history of hypertension, current use of statins was associated with a reduced risk of RCC in women. Similar direction of inverse association was found in men with no history of hypertension, although the corresponding RR was not statistically significant.

Finally, we evaluated the associations between regular use of statin drugs and overall kidney cancer risk (198 cases in women and 136 in men), including renal pelvis and ureter tumors in addition to RCC, the results were similar to those for RCC (data not shown).

DISCUSSION

In these large prospective studies, we found some suggestion that current use of statins was associated with a reduced risk of RCC among women. The association was statistically significant among women with no history of hypertension. In men, there was a suggestion of reduced risk only among those with no history of hypertension. We also found that duration of statin use was not associated with RCC risk.

Experimental data suggested that statins can suppress proliferation, induce apoptosis and inhibit metastasis of RCC in murine model [28, 29]. One of the hallmark of cancer is enhanced angiogenesis and RCC is one of the most angiogenic tumors [30]. Current available data suggest that statins have both pro- and anti-angiogenic properties and it is possible that both these opposing effects on tumor vessels growth explain the overall null result in our study on the increased RCC incidence [31]. On the other hand, and despite an anti-proliferative effect, statins can exhibit immune tolerance-promoting properties, suggesting an opposing effect on tumor development[32]. There have been 2 case-control studies [10, 11], one cohort study [12], and a subgroup analysis for one clinical trial [13] which did not find an association between statin use and RCC risk. However, two[11, 13] of the studies had sample sizes of <50 RCC cases, thus had limited statistical power to detect any association. Only one of the studies provided gender-specific results, which were non-significant[12]. On the other hand, a decreased risk of RCC (odds ratio=0.52, 95% CI=0.45–0.60) was found in a nested case-control study of US veterans with 1,446 RCC cases [7]. More than 90% of the participants of the study were male veterans. Another nested case-control study among patients with cardiovascular disease [8] also reported a significantly reduced risk of kidney cancer (odds ratio=0.27, 95% CI=0.08–0.95) with 101 cases of kidney cancer. However, in a cohort study, Friedman et al. [9] reported a 23% increased risk of kidney cancer associated with use of statins in men (n=135) but not in women (n=51) in the U.S. Therefore previous data on statin use and RCC risk were limited, mixed, and inconclusive. Most of these prior studies except one[12], did not adjust for history of hypertension which was a strong confounder of the association between statin use and RCC risk in our study. Because hypertension is a strong risk factor for RCC and strongly correlated with use of statins, it is an important confounder of the association between statins and RCC and needs to be taken into account. Our investigation of two prospective studies supports some inverse association between statin use and RCC risk, especially among women and those with no history of hypertension.

Our study had some limitations. First, despite the fact that our study participants were registered nurses and male health professionals who were familiar with prescription drugs, there was a potential -though minimal- misclassification of statin use due to the use of self-reported data. However, exposure misclassification due to inaccurate self-reporting should not be different with respect to diagnosis of RCC because the cancer analysis was made prospectively. Further misclassification of exposure could be introduced because we considered any use of cholesterol-lowering drugs to represent statin use in certain period of the follow-up (e.g., prior to 2000) in the analysis. However, >90% of participants in both cohorts who reported use of cholesterol-lowering drugs used statins. There is also little evidence to support an association between non-statin lipid-lowering drugs and RCC risk. Thus it is unlikely that such misclassification could have significant impact on our estimates. The existence of exposure misclassification would make our estimation more conservative (toward null) and may not explain the associations we found. Second, our study was limited by relatively small number of exposed cases and the absence of information on the potency,

hydrophobic status, and dosage of statins, which limited our ability to precisely examine any dose-response relationship and to differentiate the effect between lipophilic versus hydrophilic statins, as the later class may be more likely to be carcinogenic. Third, although confounding by indication may not be entirely ruled out, it is unlikely to bias the association because increased serum cholesterol levels are unrelated to risk for RCC [15]. Fourth, we lacked information on potential confounders such as family history of kidney cancer. Finally, our study population is largely white, and our results may not be generalizable to other racial populations, although there is no reason to assume that the association would be different biologically by race.

We also had several strengths in our study. First, the prospective design avoided biases related to case-control studies including biased recall of statin use. We also took advantage of repeated measures of statins use over a long follow-up period, which was a unique feature of our study to minimize misclassification of statin use and enabled us to evaluate both baseline and updated use of statins. Finally, we had information on many suspected and known risk factors of RCC including history of hypertension which turned out to be an important confounder and took it into consideration in multivariate analyses.

In summary, these prospective data provided some evidence of beneficial effect of statin use on RCC risk, especially among women. Further analysis with longer duration of follow-up and more accurate exposure assessment is required to address: 1) the diverse anti-tumor effects in men and women; 2) the effect of different type and dosage of statin on RCC risk.

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Table 1

Age-standardized characteristics of participants of the Nurses' Health Study and the Health Professionals Follow-up Study by regular use of statin drugs in 2000

Characteristics	Regular use of statin drugs			
	Women		Men	
	No (n=55,711)	Yes (n=15,341)	No (n=23,011)	Yes (n=6,867)
% statin users	78	22	77	23
Current smoker (%)	9	9	5	4
Past smoker (%)	45	49	47	54
Parity (number of childbirth)	3	3	NA	NA
History of hypertension (%)	45	66	33	49
History of diabetes (%)	7	16	5	10
Non-aspirin NSAIDs use (%)	25	29	25	28
Mean				
Age (years)	66	68	65	67
Current BMI (kg/m^2)	27	28	26	27
Physical activity (METs/wk)	17	15	34	31
Alcohol consumption, (g/day)	5	4	10	10
Total fruits (servings/day)	2	2	3	2
Total vegetables (servings/day)	2	2	3	3

*Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meter squared); METs, metabolic equivalent values for activities; NA, not applicable; NSAIDs, non-steroidal anti-inflammatory drugs

**Except for the data on mean age and % users, all data are standardized to the age distribution of each cohort

Table 2

Relative risk (RR) and 95% confidence intervals (CIs) of renal cell cancer in relation to current use of statin drugs in the Nurses' Health Study (1994–2008) and the Health Professionals Follow-Up Study (1990–2006)

Study cohort	Current use of statin drugs	
	No	Yes
Women		
Number of cases	128	36
Age-adjusted RR	1.0	0.85 (0.58–1.24)
Age & hypertension adjusted RR	1.0	0.75 (0.51–1.10)
Multivariate* RR	1.0	0.68 (0.46–1.00)
Men		
Number of cases	83	30
Age-adjusted RR	1.0	1.41 (0.91–2.17)
Age & hypertension adjusted RR	1.0	1.21 (0.78–1.88)
Multivariate* RR	1.0	1.17 (0.75–1.82)

*Adjusted for smoking status (never, 1–19, 20–39, ≥40 pack-years), body mass index (<25, 25–26.9, 27–29.9, ≥30 kg/m^2), history of hypertension (yes/no), history of diabetes (yes/no), physical activity (quintiles), fruit intake (continuous), vegetable intake (continuous), alcohol intake (continuous), and duration of regular non-aspirin NSAIDs use (no use, >0-<4, 4-<10, ≥10 years), and parity (nulliparous, 1–2, 3, 4, 5+ children) in women.

Table 3

Relative risk (RR) and 95% confidence intervals (CIs) of renal cell carcinoma according to history of regular use of statin drugs in the Nurses' Health Study (1994–2008) and the Health Professionals Follow-Up Study (1990–2006)

Variable	Never users	Ever users	Duration of use	
			< 4 years	≥ 4 years
Women				
Number of cases	118	46	21	25
Age-adjusted RR	1.0	0.96 (0.67–1.36)	0.90 (0.56–1.44)	1.02 (0.65–1.60)
Age and hypertension – adjusted RR	1.0	0.85 (0.59–1.21)	0.80 (0.50–1.28)	0.89 (0.56–1.41)
Multivariate* RR	1.0	0.76 (0.53–1.10)	0.75 (0.47–1.21)	0.77 (0.49–1.23)
Men				
Number of cases	82	31	11	20
Age-adjusted RR	1.0	1.26 (0.81–1.94)	0.93 (0.49–1.76)	1.60 (0.94–2.70)
Age and hypertension adjusted RR	1.0	1.07 (0.69–1.66)	0.80 (0.42–1.53)	1.34 (0.79–2.29)
Multivariate* RR	1.0	1.03 (0.66–1.60)	0.80 (0.42–1.53)	1.25 (0.73–2.14)

* The models were adjusted for the same covariates as the multivariate model in Table 2.

Table 4

Multivariate* relative risk and 95% confidence intervals (CIs) of renal cell cancer in relation to current use of statin drugs by history of hypertension in the Nurses' Health Study (1994–2008) and the Health Professionals Follow-Up Study (1990–2006)

Study cohort	Current use of statin drugs	
	No	Yes
Women		
Without hypertension (n=55)	1.0 (n=52)	0.28 (0.09–0.92) (n=3)
With hypertension (n=109)	1.0 (n=76)	0.83 (0.54–1.28) (n=33)
Men		
Without hypertension (n=44)	1.0 (n=40)	0.53 (0.18–1.53) (n=4)
With hypertension (n=69)	1.0 (n=43)	1.49 (0.87–2.54) (n=26)

* The models were adjusted for the same covariates as Table 2 except history of hypertension.