Statin Use and Risk of Basal Cell Carcinoma

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Abstract

OBJECTIVE—We examined the association between statin use and basal cell carcinoma (BCC) risk.

METHODS—We identified all members of a large integrated healthcare delivery system diagnosed with a histologically-proven BCC in 1997. Subsequent BCCs were identified through 2006 from health plan electronic pathology records. Longitudinal exposure to statins and other lipid-lowering agents was determined from automated pharmacy records. We used extended Cox regression to examine the independent association between receipt of statin therapy (ever vs. never, cumulative duration) and risk of subsequent BCC. To minimize confounding by indication, we conducted sensitivity analyses in the subset of individuals considered eligible for lipid-lowering therapy based on national guidelines.

RESULTS—Among 12,123 members diagnosed with BCC who had no prior statin exposure, 6381 developed a subsequent BCC during follow-up. Neither ever use of statins (adjusted hazard ratio [aHR] 1.02, 95% CI: 0.92-1.12) or cumulative duration of statin (aHR 1.02 per year, 95% CI: 0.99-1.11) was associated with subsequent BCC after adjustment for age, sex, and healthcare utilization. Risk estimates did not change appreciably when the analysis was limited to the subset of individuals who met eligibility criteria for initiating statin therapy. There was also no significant

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association between use of non-statin antilipemics and subsequent BCC (aHR 1.10, 95% CI: 0.76-1.58).

LIMITATIONS—No information was available for BCC risk factors, such as sun sensitivity and sun exposure.

CONCLUSIONS—Among a large cohort of individuals with BCC, statin therapy was not significantly associated with risk of subsequent BCC.

INTRODUCTION

Basal cell carcinoma (BCC) is the most common cancer in the U.S., affecting nearly one million Americans annually[1] and its incidence is rising.[2,3] Although BCCs are rarely fatal, their high incidence and the frequent occurrence of new primary BCCs in affected individuals[4] can cause significant morbidity. BCCs also pose a substantial financial impact and are among the most costly cancers to treat in the Medicare population.[5] The primary known risk factors for BCC are sun sensitivity and exposure to ultraviolet (UV) radiation. To date, no effective, well-tolerated chemopreventive agents exist for BCC. Such therapies would be especially useful for individuals with a prior BCC given that nearly 44% go on to develop a subsequent BCC over a 3-year follow-up period.[6]

HMG-CoA reductase inhibitors (statins) are lipid-lowering drugs that effectively reduce cardiovascular risk and are the most commonly prescribed medication in the U.S.[7] Statins have also been explored for other potentially beneficial health effects, including chemoprevention. Laboratory data support the possible role of statins for the chemoprevention of BCCs. Statin-induced cholesterol depletion induces apoptosis of cultured keratinocyte cell lines.[8] They also inhibit the sonic hedgehog signaling pathway[9-10] which is the pivotal molecular pathway in BCC carcinogenesis.[11] Statins have also been shown to have potent inhibitory effects on cancer cells *in vitro* and in animal models,[12-13] but clinical studies on cancers other than skin cancer have reached mixed conclusions.[14-17] Based on these laboratory and epidemiologic data, we hypothesized that statin use would be associated with a reduction in risk of BCCs in a population at high-risk for their development. We tested this hypothesis in a large integrated healthcare delivery system by examining the relation between statin therapy and risk of subsequent BCC among a large cohort of Kaiser Permanente of Northern California (KPNC) members previously diagnosed with BCC.

METHODS

We conducted a longitudinal cohort study of all KPNC members diagnosed with a BCC in 1997 to examine the association between statin exposure and subsequent BCC risk. In secondary analysis, we limited the cohort to those members who were eligible for statin treatment to minimize confounding by indication. Finally, we examined exposure to non-statin antilipemics and risk of subsequent BCC using the full cohort to assess whether any associations were statin-specific or related to the lowering of cholesterol levels.

Study Population

We identified all KPNC members with a histologically proven BCC from electronic health plan pathology records with an assigned SNOMED code of 809XX - 811XX (with the exception of 81000 and 81100), 80003, or 80103 and who also had a pathology report that contained the text-string "basal cell carcinoma" or "BCC" in the diagnosis line and the topography code of "skin." In 1997, we identified 18,305 BCCs diagnosed in 13,063 individuals. We excluded individuals who had medical record numbers that could not be matched to their membership file or had missing key membership information (n=55) and members who did not have active status at the time of BCC diagnosis (n=98), leaving 12,910

individuals for analysis. This study was approved by the Kaiser Foundation Research Institute Institutional Review Board.

Exposure to Statin Therapy

Longitudinal exposure to statin therapy was ascertained for each cohort member using information found in automated KPNC pharmacy databases on filled prescriptions between the index BCC diagnosis date through December 2006. We searched for all known available statins during the study period: lovastatin, simvastatin, atorvastatin, pravastatin, fluvastatin, and cerivastatin. We assigned periods of continuous statin exposure during follow-up for all cohort members using data from serial prescriptions based on each prescription's fill date, days supply of pills dispensed, and estimated days supply.[18] For any two consecutive prescriptions, we considered an individual as continuously receiving statins if the gap between the expected end date of the first prescription and fill date of the second prescription was ≤30 days. If the gap was >30 days, the individual was considered off statins until the fill date of the next prescription. Individuals who had any documented continuous statin exposure before the index date were excluded from all models (n=787).

Follow-up and Outcome

Subjects were followed from the date of their first diagnosis in 1997 until any of the following occurred: subsequent BCC, disenrollment from the health plan membership defined as a gap of more than 90 days, death, or the end of the study period on December 31, 2006. The primary outcome was subsequent BCC identified from health plan pathology records screened up to each subject's censoring date using the same SNOMED codes defined for study entry.

Covariates

Age and sex were ascertained from administrative databases. Because we hypothesized that individuals receiving statins were more likely to use the healthcare system overall and more likely to visit a dermatologist who would biopsy their tumor, we assessed health care utilization to account for possible screening bias. Health care utilization was defined as an annualized rate of medical outpatient and emergency room visits during the follow-up period. Annualized dermatology-specific healthcare utilization was also ascertained, with the assumption that dermatology visits would be where biopsies of BCCs were most likely to occur. However, results did not change when adjusting for dermatology-specific resource utilization, so only results that accounted for differences in overall health care utilization are described.

Statistical Analysis

We examined the potential impact of statins on subsequent BCC risk with two different measures of statin exposure using an extended Cox regression to account for time-dependent variables and immortal time bias.[18] First, we used an "ever vs. never use" approach in which we assigned persons who initiated statin therapy as being continuously on statins through the follow-up period starting with the first prescription lasting at least 30 days filled on or after index date and evidence of at least one refill. If an individual initially filled only a single prescription but no refills, we assumed that the individual had not taken the pills as prescribed due to problems with side effects or other reasons, and these individuals were considered unexposed (n=31). Second, to investigate the possible effect of duration of exposure on subsequent BCC, we calculated the cumulative days supply of statin therapy during follow-up. Cumulative exposure was calculated by determining the date on which each exposed cohort member reached an additional year of statin exposure. Cumulative exposure was also examined by categories: unexposed, short-term (1 day-2 years), moderate (>2-5 years), and long-term (>5 years) use. In addition, we performed separate sensitivity analyses varying the lag time before exposure to statins would be considered to have an impact on BCC formation (0 or 90

days), as well as including cases of very early occurrence of subsequent BCC (≤90 days after index date), and late occurrences (over 180 days and over 365 days after index date).

To assess whether the exposure was statin-specific or related to the lowering of cholesterol levels by other pharmacological methods, we also examined exposure to non-statin anti-lipemics. Given the limited number of cohort members who took these agents in the absence of concomitant statin therapy, we only used an "ever vs. never use" approach. In addition, for this analysis, we excluded observation time for any individual after the date they began use of statins.

Finally, to further address the possibility of residual confounding by indication, we identified the subset of cohort members who were eligible for lipid-lowering therapy based on national clinical practice guidelines[20] during the study period and who did not have prior known statin therapy. We repeated all analyses in this subset for comparison with the main results.

RESULTS

Cohort Characteristics

Among 12,910 individuals diagnosed with BCC, 787 had known statin exposure at cohort entry and were excluded, leaving 12,123 subjects for analysis. Mean age was 64.7 ± 14.1 years and 58.9% were men. Of the 12,123 subjects, 3309 (27.3%) were lost to follow-up during the 10 year period. The mean age of those members who were lost to follow-up (66.03 years) and their gender distribution (58.4 % male) did not substantially differ from the demographics of the full cohort. During follow-up, 1,535 subjects received statin therapy, and there was no significant difference in gender (59.1% male exposed vs. 58.8% male unexposed, p=0.85). The mean number of years of follow-up was 4.24 years (median 3.14 years). Mean age at entry was slightly but significantly (p=0.01) higher in the stain-exposed (65.3 years) than in the statin-unexposed (64.6 years) patients. The median number of statin prescriptions filled per treated individual during follow-up was 10 (interquartile range: 5-18) with median 828 days of exposure (interquartile range 392-1460). The most commonly prescribed statins were lovastatin (75.2%), simvastatin (19.9%), atorvastatin (3.9%), pravastatin (0.8%), simvastatin/ezetimibe (0.1%) and fluvastatin (0.1%).

Overall, only 120 cohort members received non-statin antilipemics, which included gemfibrozil (47.1%) niacin (26.0%), cholestyramine (13.6%), colestipol (6.3%), ezetimibe (4.2%), niacinamide (0.3%) and fenofibrate (2.4%). The median number of non-statin antilipemic prescriptions filled per treated individual during follow-up before the use of any statins was 5.0 (interquartile range: 2.0-10.0) with median 242 (interquartile range 97.5-513.0) days of exposure.

Statin Therapy and Subsequent BCC Risk

A subsequent BCC diagnosed more than 90 days after index date was observed in 6,381 subjects, with 83.4% occurring during the first five years of follow-up. Using an ever vs. never approach, statin use was associated with a 16% higher risk of BCC (P=0.004, Table 1). However, after adjustment for age, gender, and healthcare utilization, the results were no longer statistically significant (adjusted hazard ratio [aHR] 1.02, 95% CI: 0.90-1.12). A sensitivity analysis which included all subsequent BCCs starting one day after index date demonstrated similar results (aHR 1.07, 95% CI: 0.95-1.19). Additional sensitivity analyses including only those subsequent BCCs occurring over 180 days and over 365 days after the index date did not alter the results (data not shown). Similarly, sensitivity analysis adding a 90-day lag time before statins would have an impact on BCC formation did not alter the results (aHR 1.00, 95% CI: 0.90-1.11).

Cumulative Statin Exposure and Subsequent BCC

For each additional year of statin exposure, there was no statistically significant change in subsequent BCC risk after adjusting for age, sex, and healthcare utilization (aHR 1.02, 95% CI: 0.99-1.06). Results were unchanged if the 90-day lag in statin exposure was included (aHR 1.02, 95% CI: 0.98-1.05). Sensitivity analysis that included subsequent BCC occurring anytime after index date showed a 4% increased adjusted risk of subsequent BCC per year of statin use (aHR 1.04, 95% CI: 1.00-1.08) that was of borderline statistical significance.

To further clarify the effect of treatment duration on subsequent BCC risk, we categorized cumulative statin exposure. We observed larger point estimates of increased risk for subsequent BCC with increasing duration of exposure to statins compared with no use, but the differences were not statistically significant: short-term use (aHR 0.98, 95% CI: 0.87-1.11), moderate use (aHR 1.05, 95% CI: 0.88-1.24) and long-term use (aHR 1.30, 95% CI: 0.93-1.81, p=0.20 for linear trend). Sensitivity analyses that either included all subsequent BCCs occurring anytime after index date or adding a 90 day statin lag did not alter our results (data not shown).

Statin use and BCC risk in treatment-eligible patients

We repeated all analyses in the subset of individuals who met criteria to receive lipid-lowering therapy based on national clinical practice guidelines incorporating data on low-density lipoprotein cholesterol level and the presence of cardiovascular risk factors[20] to further limit potential confounding by indication. Of the 1744 subjects included in the analysis, 382 (21.9%) were lost to follow-up. The mean number of years of follow-up was 4.21 years (median 3.40 years). After adjustment for age, gender and health care healthcare utilization, there was no significant association between statin use or duration of statin use and BCC risk in this treatment-eligible subset (Table 1).

Other lipid-lowering agents and Subsequent BCC

We also examined the association between use of non-statin antilipemic agents and subsequent BCC. Of the 11932 subjects, 3262 (27.3%) were lost to follow-up. The mean number of years of follow-up was 4.25 years (median 3.45 years). After adjustment for age, sex and health care utilization, there was no significant relation between any use of non-statin lipid-lowering drugs and subsequent BCC risk (aHR 1.10, 95% CI: 0.76-1.58).

DISCUSSION

In a large cohort of individuals at high risk for BCC, we did not observe any significant association between statin exposure and risk of subsequent BCC. The observed crude risk of subsequent BCC was noted to be higher with both any use of statin therapy and with increasing duration of treatment, although these associations were attenuated after adjustment for age, sex and health care utilization. These results were consistent in the overall cohort and in the subset of patients who met national guidelines for eligibility for lipid-lowering therapy. The results were also robust to other sensitivity analyses that assessed different methods of classifying statin exposure (lag 0 vs. 90 days), and identifying subsequent BCCs (arising within 1 day vs. >90 days of the index date). In addition, we did not observe any significant association between receipt of non-statin anti-lipemic agents and risk of subsequent BCC, although those analyses had limited power given the infrequent use of these agents in our population.

Studying the epidemiology of non-melanoma skin cancer is difficult because unlike most malignancies, they are not systematically reported to centralized cancer registries. A unique strength of our study was the leveraging of data within a large integrated health care delivery system that included electronic capture of all pathology reports, making it feasible to study the epidemiology of non-melanoma skin cancers. The automated health plan pharmacy database

facilitated accurate quantification of longitudinal exposure to statin therapy over time, minimizing recall bias. Our follow-up period of up to ten years also allowed assessment of potential long-term effects of statin use on cancer risk. Importantly, our study design focused on a cohort of patients who were previously diagnosed with BCC before the widespread use of statins. This approach mitigates the lack of systematic data on risk factors that contribute to the initial development of BCC such as sun sensitivity, skin type, and history of sun exposure. Finally, we conducted multiple sensitivity analyses that varied cohort and statin exposure definitions, all of which yielded consistent results.

Our findings are consistent with clinical outcome data from several large randomized placebo-controlled trials of statin use for cardiovascular endpoints which observed a slightly increased risk of non-melanoma skin cancer with statin therapy,[21-24] although the results did not reach statistical significance. In contrast, a recently published article analyzing cancer outcome data from three statin trials did not observe any increased risk of skin cancer.[25] These trials were designed to assess cardiovascular endpoints rather than non-melanoma skin cancer, which were not systematically ascertained, and the trials were likely underpowered to detect a possible association with statin use.

Selected lines of evidence support the hypothesis that statins may increase the risk of BCC. Statins have been shown to enhance UV phototoxicity in human skin cell lines, an effect that was reversed with cholesterol supplementation.[26] Certain statins have been associated with UVB phototoxicity.[27] Also, Smith-Lemli-Opitz syndrome which is characterized by a mutation in the enzyme involved in the last step of cholesterol biosynthesis is associated with marked UVA photosensitivity.[28] Alternatively, statins could exert possible carcinogenic effects by inhibiting lymphocyte function,[29] thereby altering immune surveillance. In rodents, statins have also been shown to cause cancer in selected studies at exposure levels comparable with those used in humans.[30]

Our study had several limitations. We relied on information from filled prescriptions to characterize statin exposure and were unable to directly measure drug use, which may lead to misclassification. Cohort members may have filled their prescriptions for statins outside a health plan pharmacy, although use of non-Kaiser pharmacies by health plan members is estimated to be rare.[31] We were not able to examine possible differences between individual statins given that the majority of treated patients received lovastatin. Information about sun exposure history was unavailable, although we attempted to minimize the impact of this by selecting a cohort of patients who by virtue of having one BCC in 1997, shared common risk factor profiles that would make them at similarly increased risk for subsequent BCC. We attempted to control for possible screening bias by adjusting for overall healthcare utilization. We also accounted for confounding by indication by performing a secondary analysis among the subset of patients who appeared eligible for statin therapy based on national clinical practice guidelines.

As an observational study of clinical practice, we cannot completely exclude residual confounding or other treatment selection biases as an alternative explanation of our findings. It is also possible that a small number of subsequent BCCs were treated outside of health plan facilities that were not captured by our pathology database. However, since cohort members already had at least one BCC treated at health plan facilities, it is unlikely that subsequent BCCs would be treated outside the health plan or that this would differ by statin treatment status. Finally, as our study was conducted among insured adults in Northern California, our results may not be completely generalizable to uninsured persons and other health care or geographic settings.

In conclusion, we found that statin exposure was not associated with a lower risk of subsequent BCC. Point estimates were suggestive of potential higher risk with statin therapy although not statistically significant. Our study detects no association between use of statins, the most commonly prescribed medications in the U.S., and risk of subsequent BCC, the most common cancer.[1,7] Given the ubiquitous and growing use of statin therapy and the public health relevance of BCC, additional studies are needed to clarify the relationship of statins to these cancers.

Acknowledgments

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Table 1

Statin Use, Non-statin antilipemics use and subsequent BCC risk in full cohort and sub-cohort (statin eligible)

Analysis Model	HR unadjusted	95% CI	p-value	HR Adjusted[*]	95% CI	p-value
Full Cohort: Statin use						
Eve/Never						
Unexposed[**] (n=10588)	1.000	Referent		1.000	Referent	
Exposed (n=1535)	1.156	(1.048,1.276)	0.0038	1.016	(0.920,1.122)	0.752
Cumulative[◊] (n=12,123)	1.062	(1.028,1.097)	0.0003	1.023	(0.990, 1.057)	0.180
Categorical cumulative						
Unexposed[**] (n=10588)	1.000	Referent		1.000	Referent	
Short-term (n=677)	1.110	(0.985, 1.250)	0.0861	0.981	(0.871, 1.106)	0.7571
Moderate (n=605)	1.200	(1.013, 1.420)	0.0347	1.047	(0.884, 1.241)	0.5923
Long-term (n=253)	1.546	(1.108, 2.157)	0.0104	1.299	(0.930, 1.814)	0.1246
	Trend		*0.0006*	*Trend*		*0.1958*
Statin eligible Sub-Cohort: Statin use						
Ever/Never						
Unexposed[**] (n=1266)	1.000	Referent		1.000	Referent	
Exposed (n=476)	1.102	(0.925, 1.312)	0.2768	1.067	(0.896, 1.270)	0.4685
Cumulative[◊] (n=1742)	1.055	(0.997, 1.117)	0.0642	1.048	(0.990, 1.110)	0.1031
Categorical cumulative						
Unexposed[**] (n=1266)	1.000	Referent		1.000	Referent	
Short-term (n=198)	1.040	(0.847, 1.276)	0.7089	1.002	(0.816, 1.229)	0.9863
Moderate (n=189)	1.216	(0.918, 1.610)	0.1721	1.192	(0.901, 1.577)	0.2193
Long-term (n=89)	1.380	(0.809, 2.354)	0.2373	1.329	(0.779, 2.266)	0.2967
	Trend		*0.0992*	*Trend*		*0.1522*

Analysis Model	HR unadjusted	95% CI	p-value	HR Adjusted[*]	95% CI	p-value
Full Cohort: Non-statin antilipemics use						
Ever/Never						
Unexposed[**] (n=11812)	1.000	Referent		1.00	Referent	
Exposed (n=120)	1.189	(0.825, 1.714)	0.352	1.098	(0.762, 1.582)	0.6165

[*] Adjusted for age, gender and average medical visits per year of follow-up

[**] No statin prescriptions with at least one refill at KPNC pharmacies during follow-up

◊ Risk per one additional year cumulative statin exposure