Published in final edited form as:

Ann Intern Med. 2009 January 6; 150(1): 9–18.

Association Between Statin Use and Risk for Keratinocyte Carcinoma in the Veterans Affairs Topical Tretinoin Chemoprevention Trial

David D. Dore, PharmD, PhD, Kate L. Lapane, PhD, Amal N. Trivedi, MD, MPH, Vincent Mor, PhD, and Martin A. Weinstock, MD, PhD

From i3 Drug Safety, Waltham, Massachusetts; The Warren Alpert Medical School of Brown University, Providence Veterans Affairs Medical Center; and Rhode Island Hospital, Providence, Rhode Island; and Virginia Commonwealth University, Richmond, Virginia

Abstract

Background—Recent evidence suggests that statins may prevent cancer.

Objective—To quantify the association between statin use and the occurrence of keratinocyte carcinoma in high-risk veterans.

Design—Cohort study.

Setting—6 Veterans Affairs medical centers.

Participants—1037 participants of the Veterans Affairs Topical Tretinoin Chemoprevention Trial, a randomized, multicenter, double-blind, vehicle-controlled trial of topical tretinoin, 0.1%, for prevention of keratinocyte carcinoma conducted from November 1998 to November 2004.

Measurements—Time to first occurrence of keratinocyte carcinoma on the face or ears. Participants using a statin at randomization, according to the Veterans Affairs Pharmacy Benefits Management database, were considered exposed. Study dermatologists conducted physical examinations at baseline and every 6 months during follow-up. The association between statin use at randomization and the outcome was evaluated by using propensity score matching ($n = 608$) and Cox proportional hazards regression ($n = 1037$).

© 2009 American College of Physicians

Requests for Single Reprints: David D. Dore, PharmD, PhD, i3 Drug Safety, 950 Winter Street, Suite 3800, Waltham, MA 02451; david.dore@i3drugsafety.com.

Current Author Addresses: Dr. Dore: i3 Drug Safety, 950 Winter Street, Suite 3800, Waltham, MA 02451.

Drs. Lapane, Trivedi, and Mor: Brown University, Box G-ST, 121 South Main Street, Providence, RI 02903.

Dr. Weinstock: Dermatoepidemiology Unit, Veterans Affairs Medical Center, 111D, 830 Chalkstone Avenue, Providence, RI 02908.

Current author addresses and author contributions are available at www.annals.org.

Potential Financial Conflicts of Interest: *Consultancies:* D.D. Dore (Pfizer). *Grants received:* K.L. Lapane (Pfizer).

Reproducible Research Statement: *Study protocol and statistical code:* Available from Dr. Dore (david_dore@brown.edu). *Data set:* Not available.

Author Contributions: Conception and design: D.D. Dore, K.L.

Lapane, V. Mor, M.A. Weinstock.

Analysis and interpretation of the data: D.D. Dore, K.L. Lapane, A.N. Trivedi, M.A. Weinstock.

Drafting of the article: D.D. Dore.

Critical revision of the article for important intellectual content: D.D. Dore, K.L. Lapane, A.N. Trivedi, V. Mor, M.A. Weinstock.

Final approval of the article: D.D. Dore, K.L. Lapane, A.N. Trivedi, V. Mor, M.A. Weinstock.

Provision of study materials or patients: M.A. Weinstock.

Statistical expertise: D.D. Dore, K.L. Lapane.

Obtaining of funding: M.A. Weinstock.

Administrative, technical, or logistic support: D.D. Dore, K.L. Lapane, V. Mor, M.A. Weinstock.

Results—Among the 1037 participants, 37% used a statin at randomization ($n = 397$) for a median duration of at least 900 days over a median follow-up of 3.5 years. In the propensity score-matched analysis, statin use at randomization was not associated with keratinocyte carcinoma (rate ratio, 0.92 [95% CI, 0.73 to 1.16]), a finding that was consistent with the estimates derived from the Cox proportional hazards regression (rate ratio, 0.84 [CI, 0.70 to 1.02]).

Limitations—The extent of residual confounding is unknown, and the confidence bounds around the measures of association were wide. These data may not be generalizable to lower-risk populations.

Conclusion—These data show no conclusive or consistent relationship between long-term statin use and risk for keratinocyte carcinoma.

Funding—Department of Veterans Affairs, Agency for Healthcare Research and Quality, American Cancer Society, and National Institutes of Health.

Keratinocyte carcinoma consists of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) and is the most common cancer in the United States, with more than 1 million cases occurring in 2006 (1). Basal cell carcinoma causes substantial illness, including local tissue destruction and disfigurement (2, 3). Squamous cell carcinoma metastasizes more frequently than BCC, leading to an elevated mortality risk, particularly in elderly persons (4, 5). Few effective strategies exist for preventing keratinocyte carcinoma. The most important preventive measure is regular sunscreen use (6).

Statins reduce cardiovascular morbidity and mortality (7–11) but are pharmacologically pleiotropic, with preliminary evidence showing beneficial effects in other diseases, including dementia (12, 13), fractures (14, 15), and multiple sclerosis (16, 17). Statins may also prevent cancer by inhibiting the mevalonate pathway (18, 19). This pathway promotes synthesis of downstream nonsterol isoprenoid derivatives that may block apoptosis and promote tumor growth, angiogenesis, and tumor metastasis (20–23). Data on whether statins prevent cancer have been inconclusive, with some studies showing no effect (24) and others suggesting that they are beneficial (25). These conflicting findings may be due in part to varying effects of statins on cancer in different tissue types or locations (26).

We aimed to estimate the association between statin use and new lesions of keratinocyte carcinoma in the Veterans Affairs (VA) Topical Tretinoin Chemoprevention (VATTC) trial sample. The trial followed participants closely and provided standardized and complete assessments of outcomes and potential confounders.

Methods

Setting and Participants

We conducted a cohort study by linking data from the VATTC trial and the VA Pharmacy Benefits Management database. Details of the VATTC trial have been published elsewhere (27, 28). The VATTC was a randomized, multi-center, double-blind, vehicle-controlled trial of topical tretinoin, 0.1%, applied to the face and ears for prevention of keratinocyte carcinoma in high-risk veterans conducted from November 1998 to November 2004 at 6 VA medical centers. The study centers were chosen for participation on the basis of factors related to their suitability for serving as centers in the overall randomized trial but were geographically distributed throughout the United States. The 6 locations were Chicago, Illinois; Durham, North Carolina; Miami, Florida; Long Beach, California; Phoenix, Arizona; and Oklahoma City, Oklahoma. Table 1 lists the trial's exclusion criteria.

Eligible veterans were at least 18 years of age, received care at 1 of the 6 participating VA centers, and had 2 or more keratinocyte carcinomas in the 5 years before enrollment ($n = 1131$). Study personnel received signed informed consent from all participants before enrollment. The 8 relevant institutional review boards approved the study protocol and procedures. We excluded 52 participants without pharmacy claims in the Pharmacy Benefits Management database. We also excluded 42 participants who initiated statin therapy during follow-up, leading to a final sample of 1037 veterans (Figure 1).

Outcome Ascertainment

The primary outcome was the first occurrence of keratinocyte carcinoma (BCC or invasive SCC) on the face or ears. We did not count recurrent lesions. We chose to combine BCC and SCC, despite certain etiologic differences (such as lag time after ultraviolet exposure, association with genetic mutations, and relation to immunosuppression and human papillomavirus exposure), because they are both skin cancers derived from epidermal cells, the primary cause of both is ultraviolet sun exposure, and their therapies (both pharmacologic and surgical) are nearly identical. Because of the similarities of BCC and SCC, we hypothesized that the statins would penetrate each type of cancer equally, leading to similar pharmacologic activity across tumor types and a similar reduction in the rate of BCC and SCC that would be only minimally affected by their etiologic differences.

Study dermatologists conducted physical examinations at baseline and every 6 months during follow-up. One of 2 central reference dermatopathologists read each biopsy specimen of the face and ears. Both central dermatopathologists read 10% of all biopsy specimens for a VATTC reliability substudy (27), which showed high reliability for diagnosis of BCC ($\kappa = 0.88$) and substantial agreement for diagnosis of invasive SCC ($\kappa = 0.62$) (Appendix Table, available at www.annals.org).

Exposure to Statins

We derived medication use information from the VA Pharmacy Benefit Management database for VATTC participants who used an outpatient VA pharmacy from 29 September 1998 to 15 November 2004. The Pharmacy Benefits Management database contains claims for all prescription transactions from every VA site (29). More than 99% of prescriptions in the Veterans Health Information Systems and Technology Architecture—the VA gold standard—are recorded in the Pharmacy Benefits Management database (4). We matched the Pharmacy Benefits Management data to VATTC data.

We categorized participants according to their use of statins at their randomization date. We considered participants exposed if they had used any statin (simvastatin, atorvastatin, fluvastatin, lovastatin, or pravastatin) at the date of randomization, although under the VA system at the time, simvastatin and lovastatin were the primary agents used. Because participant accrual occurred throughout the first 4 years of the trial, we had a varying amount of pharmacy claims available before each person was randomly assigned, but had no data before 1998. We hypothesized that statin use at randomization represented long-term use, an assumption supported by an analysis of duration of use on the basis of the available data. Forty-two participants initiated statin therapy during VATTC follow-up. We excluded initiators because we considered the duration of statin use to be too short to have an effect on the outcome and because there were too few initiators to estimate an effect of short-term use reliably.

We estimated the average daily dose of statins by dividing the product of the dose per tablet and the dispensed quantity by the total days of supply dispensed for each prescription claim. We assumed that simvastatin, atorvastatin, fluvastatin, and pravastatin are equipotent.

Potential Confounders

We considered factors that may affect risk for keratinocyte carcinoma to be potential confounders, including age; sex; race or ethnicity; education; smoking history; sun exposure history; psoriasis; eczema; inflammatory acne; rhinophyma; the number of actinic keratoses at baseline; the number of previous keratinocyte carcinomas; sunscreen use; sun avoidance behaviors; and measures of sun sensitivity, which included variables on hair color, skin color, freckling, reaction to first summer sun exposure without sunscreen, skin oiliness, the year-round presence of tan lines, and the Charlson Comorbidity Index score (30–34). We also considered use of tanning beds, chemical peels, 5-fluorouracil, immunosuppressants, nonsteroidal anti-inflammatory agents, other cholesterol-lowering medications, or angiotensin-converting enzyme inhibitors as potential confounders (35, 36). The primary VATTC intervention, topical tretinoin, did not confound our estimates; hence, it is not included in our final Cox regression and propensity score models.

The VATTC personnel ascertained measures of potential confounders at baseline and at follow-up visits, including measures of sun sensitivity and exposure. The study investigators' questions about these exposures related to various points in the participants' lives, including early childhood, adolescence, and intervals throughout adulthood (for example, age 18 years, age 40 to 60 years, or in the 5 years before enrollment). This allowed for adjustment of potential confounders that may have exerted a causal effect at different relevant etiologic periods. Baseline clinical examinations included standardized scales of photo-damage, counts and relative intensity of precancerous and other clinically relevant lesions, and questions about the average number of hours spent in the sun at different points in the participants' lives. Other questions ascertained the proportion of time spent in the sun that participants used sun-avoiding techniques (for example, wearing a hat), the annual frequency of sunburns at different life stages, and the presence of previous diagnoses (for example, eczema). During follow-up, study investigators measured what proportion of time participants used their study sunscreen, had sunburns, or were exposed to other potential keratinocyte carcinoma causes (such as tanning beds). The degree of missing data was low (approximately 2% on variables used) and varied with little omitted information in variables on demographic characteristics, smoking, previous sun exposure, and previous diagnoses, but with relatively more omitted information about family history and follow-up sun exposures.

Analytic Approach

We calculated person-time as the number of days from randomization to the first occurrence of an outcome, the date of the last study visit for those who were lost to follow-up, the date of death, or the date of study termination. The relation between statins and keratinocyte carcinoma was conceptualized a priori; however, because the primary trial evaluated another intervention, there were no formal sample size considerations for our study.

Cox Proportional Hazards Regression—We estimated the association between statin use and keratinocyte carcinoma incidence by using Cox proportional hazards regression models. To evaluate and rule out departures from the proportional hazards assumption, we plotted log–log survival functions and tested the exposure variable for an interaction with time. To evaluate confounding, we first forced age, sex, a measure of intrinsic sun sensitivity, measures of past sun exposure, variables reflecting the study centers, and cigarette smoking into the model. We then used a manual forward selection process, adding the remaining potential confounders one by one. We retained variables in the model that changed the estimated effect of statins on the occurrence of keratinocyte carcinoma by approximately 5% or more. We evaluated categorized measures of sun exposure and sun avoidance behavior at different points in the participants' lives and tested different

categorizations of these measures on the basis of empirical distributions. We further adjusted for comorbid conditions by using the Charlson Comorbidity Index (33), which we estimated by using the algorithm described by Romano and colleagues (34). We adjusted for a summary score of sun sensitivity, which was taken as the numerical average of the answers to 7 questions, each of which ranged from 0 to 1 (least to most sun-sensitive). We modeled covariates by using dummy variables for intrinsically categorical variables. Continuous variables were categorized by using clinically and empirically derived criteria and were modeled in a similar manner. By using Cox regression models, we derived crude and adjusted rate ratios and 95% CIs to estimate whether statin use was associated with a reduction in the rate of keratinocyte carcinoma.

Propensity Score Matching—We also estimated the association between statin use and the occurrence of keratinocyte carcinoma by using propensity score matching (37). We used logistic regression to estimate the probability of statin use at randomization as a function of the potential confounders. We used a non-parsimonious modeling approach and tested for interactions to maximize the discrimination of the predictive model. To maximize efficiency, we included potential confounders that may be related to the risk for keratinocyte carcinoma, regardless of whether they were associated with statin use (38). This included all variables used in the Cox regression plus additional variables that fit this criterion. The c-statistic for the predictive models was 0.71, suggesting a moderate overlap between the predicted probability distributions of statin use between users and nonusers. Successful use of propensity score matching is conditional on sufficient overlap of the propensity score distribution among the exposed and unexposed. To maximize matching within the area propensity score distribution overlap, we matched exposed and unexposed participants on the propensity score by using the greedy matching algorithm (39). The greedy algorithm uses an iterative process to identify the closest matches first and then widens the caliper for matching with each subsequent iteration. We assessed for covariate balance before and after propensity score matching by examining frequency distributions by exposure status. We compared these distributions by using chi-square tests for categorical variables and 2-sample *t* tests for continuous measures. Suitable matches were not available for 98 statin users, resulting in a propensity-matched sample of 608 veterans after 1-to-1 matching. Using this matched cohort, we estimated adjusted rate ratios and 95% CIs.

Sensitivity Analysis—To evaluate the effect of statin discontinuation during follow-up, we tested the influence of treating the exposure indicator as a time-varying covariate in the Cox regression model, which attributed statin user person-time as un-exposed after discontinuation. This approach is informative about whether our definition of statin use misclassifies actual use. Differences in the estimates between the fixed-time and time-varying models may also reflect a true biological effect of statin discontinuation; however, we hypothesized that there would be no difference between the models. We conducted analyses to evaluate the extent and effect of competing risks and loss to follow-up on the findings. We also tested the assumption of noninformative censoring by evaluating the withdrawal rate and competing risks by statin use. We conducted these analyses to evaluate the potential for bias from differential loss to follow-up.

Role of the Funding Source

The Cooperative Studies Program of the Department of Veterans Affairs, Office of Research and Development, supported the main trial and portions of this work. Veterans Affairs Cooperative Studies Program personnel participated closely in the design, data collection, and analysis of the main trial. These same personnel reviewed the manuscript. The authors conducted the design, analysis, and interpretation of the study. The Agency for Healthcare Research and Quality, the American Cancer Society, and the National Institutes of Health

provided additional support. These funding sources played no role in the design, conduct, or reporting of this study.

Results

Patient Characteristics

Among the participants, 37% used a statin at randomization. The median follow-up time was 3.5 years for statin users and 3.6 years for nonusers. The median time to first keratinocyte carcinoma or censoring was 2.1 years for statin users and 2.0 years for nonusers. Table 2 shows the characteristics of the full and propensity score–matched study populations. Nearly all study participants were non-Hispanic white men. On average, statin users were older than nonusers. Statin users scored higher on the Charlson Comorbidity Index and were more likely to use other cholesterol-lowering medications and angiotensin-converting enzyme inhibitors. Unexposed participants had higher intrinsic sun sensitivity and were more likely to have a history of eczema and use of immunosuppressant drugs. On average, the exposed and unexposed propensity score–matched groups had similar distributions of the measured covariates, including assignment to tretinoin treatment. The characteristics of participants excluded by propensity score matching were slightly different from those of the retained patients. Excluded statin users were more likely to use angiotensin-converting enzyme inhibitors and other cholesterol-lowering medications and were less likely to have a family history of keratinocyte carcinoma. Excluded nonusers were more likely to have rhinophyma, psoriasis, eczema, and a family history of BCC or SCC.

Statin Use

The average duration of statin use during the study was at least 900 days (Table 3). At least 80% of patients exposed used a statin for at least 6 months before their date of randomization. The daily dose of statins increased from an average of 18.8 mg per user for their first prescription on record to 34.0 mg for the last. More veterans took high doses of statins later in the study, with 15.4% of participants taking 60 to 80 mg/d at the end of follow-up compared with only 3.8% at randomization. A greater proportion of veterans used high-potency statins (atorvastatin and simvastatin) at the end of the study, whereas use of lovastatin decreased (Table 3).

Risk for Keratinocyte Carcinoma

Table 4 shows the crude and adjusted rate ratios from the Cox proportional hazards model ($n = 1037$). Fifty-two percent of participants had keratinocyte carcinoma during follow-up, with 42% of veterans receiving a diagnosis at least 1 BCC and 24% of at least 1 SCC. The crude incidence rate of any keratinocyte carcinoma was 234.8 per 1000 person-years. The crude incidence rates of BCC and SCC were 168.0 and 80.8 per 1000 person-years, respectively. In the unadjusted analysis, use of a statin at randomization was associated with a 17% lower rate of keratinocyte carcinoma. Adjustment by Cox regression for clinical, demographic, and medication use characteristics, including the primary trial intervention, had little effect on this finding. This reduction was evident after approximately 1 year and persisted throughout follow-up (Figure 2). The estimated rate ratios were similar to the primary estimates when evaluated for simvastatin and lovastatin separately. The use of other cholesterol-lowering medications was associated with an inconclusive decrease in the rate of keratinocyte carcinoma (rate ratio, 0.86 [95% CI, 0.66 to 1.13]). We found no evidence of an interaction between statin use at randomization and randomization to topical tretinoin in the primary trial.

In the propensity score–matched cohort ($n = 608$), use of a statin at randomization was not associated with the rate of keratinocyte carcinoma (rate ratio, 0.92 [CI, 0.73 to 1.16]) (Table

4). An analysis that treated statin exposure as a time-varying covariate to account for drug discontinuation yielded similar estimates as the fixed-time model (rate ratio, 0.83 [CI, 0.69 to 0.99]). Withdrawal rates were low and not differential by statin use (2.3% among statin users and 3.4% among nonusers). Deaths occurred in 10.6% of statin users and 11.3% of nonusers. These formal sensitivity analyses are available from the authors on request.

Discussion

In our crude model, we found that statin use at randomization was associated with a 17% lower rate of new lesions of keratinocyte carcinoma among high-risk veterans. Adjustment for individual material confounders by Cox regression did not alter this estimate. After approximately 1 year, the difference in risk remained approximately constant and was consistent for BCC and SCC separately. Results of our propensity score-matched analysis, however, suggests that statin use is not associated with the rate of keratinocyte carcinoma. Because of the width of the CIs, these data are inconclusive, but they do not refute the hypothesis that statins may prevent cancer.

Our Cox regression results are consistent with findings from a pooled analysis of clinical trials that found that use of fluvastatin was associated with a 24% reduction in the occurrence of nonmelanoma skin cancer (40). To our knowledge, no other studies have specifically shown an effect of statins on risk for keratinocyte carcinoma. Most research evaluating the effect of statins on skin cancer has focused on melanoma. A recent systematic review of randomized clinical trials showed no statistically significant reduction of melanoma incidence among users of statins and fibrates (41). Late-acting etiologic actions are more important for SCC than for BCC (30, 31), and we hypothesized that statin exposure in this study occurred late in the keratinocyte carcinoma etiologic process. The point estimate for SCC was more protective than for BCC (although not statistically separable), which is consistent with this previous knowledge.

Because our study was inconclusive, it does not refute the hypothesis that statin use is associated with a lower risk for some cancers. Indeed, recent data suggest that statins lower risk for prostate cancer (42), especially with long-term use (43) or in advanced disease (22, 44, 45), but seem to have no benefit in colorectal cancer (46, 47). However, an epidemiology study by Farwell and colleagues (48) found an approximate 25% reduction in total cancer among statin users in the Veterans Affairs New England Healthcare System data (48). Others found associations between statins and lower risk for renal cell carcinoma (49) but no association with lung and breast cancer (50).

Data on cancer incidence from large randomized trials of statins have been similarly inconclusive. A recent meta-analysis of randomized trials showed no effect of statins on cancer incidence and death (51). It is likely, however, that the studies in the meta-analysis were affected by exposure (52) and outcome (53) misclassification and insufficient follow-up time (54). The relative lipophilicity of statins may influence their cancer prevention efficacy by affecting their target-cell penetration (52). Hydrophilic agents, such as pravastatin, may not penetrate certain tumor cells, which might render them ineffective or even harmful (52). The importance of statin lipophilicity may also vary by tumor site. This argues against the notion that statin chemoprevention is a class effect. Moreover, differences in tumor site and characteristics may affect a cancer's sensitivity to statins (53). Each of these issues may have biased the results of the meta-analysis toward the null and may similarly affect individual randomized trials and epidemiology studies.

Many previous studies did not have power to assess cancer outcomes, especially at specific sites; did not rigorously measure cancer outcomes; and were not conducted in participants at

high risk for cancer (7–11). The VATTC investigators ascertained cases of keratinocyte carcinoma consistently and validly, especially for BCC and the full spectrum of SCC (27). This rigorous measurement has been unavailable in previous studies (40). Our approach decreases the possibility of outcome misclassification. However, the reliability estimates from an internal VATTC validation study suggest that, despite these efforts, there is still some error in the outcome measurement, with κ values for interrater agreement of SCC as low as 0.62 for our outcome of invasive SCC (27). Any residual misclassification is unlikely to be related to receipt of a statin or error in other variables and would therefore attenuate our estimates. In addition, BCC, which was measured with less error, accounted for most outcomes.

Statin users may be more likely than nonusers to seek the services of health professionals. This could lead to increased probability of diagnosing keratinocyte carcinoma in this group that could bias the estimate of the statin–keratinocyte carcinoma relation toward no effect. However, the VATTC investigators examined participants every 6 months and ascertained other keratinocyte carcinoma events through usual care pathology reports. This method makes this bias unlikely in our study. Assuming a true protective effect of statins, long-term users of these drugs may have been less likely to enroll in the VATTC because 1 inclusion criterion was a history of 2 or more keratinocyte carcinomas. However, because these data suggested that statin use was of long duration in the VATTC participants, selection bias by this mechanism is unlikely.

Because we used claims data to ascertain exposure, we cannot be sure that participants who received statins actually took their medication. However, recent work has shown that VA pharmacy claims accurately assess medication use (4). Our study is an improvement over previous work assessing the effect of statin use on various cancers, which may have been affected by exposure misclassification (24). However, in our study, veterans may have filled prescriptions outside of the VA pharmacy system, which could have led to underascertainment of medication use. To address the possibility that veterans could have filled prescriptions elsewhere, we included only participants who used the VA pharmacy system. This approach ensured similar completeness of drug data among the statin users and non-users. Moreover, veterans have a financial incentive to fill their prescriptions within the VA system, and evidence suggests that VA pharmacy claims are valid and reliable for ascertaining chronic disease burden (55). Any exposure misclassification by this mechanism would probably dilute our results.

Our drug use data started in September 1998. Because of this left-censoring, we could not ascertain the date of statin treatment initiation or estimate the actual duration of statin use. However, the available data suggested that statin therapy was of long duration. Results of the time-varying Cox regression model suggest that keratinocyte carcinoma is not immediately sensitive to discontinuation of a statin, which is consistent with the notion that keratinocyte carcinoma has at least a moderate-length empirical induction period and that short-term therapy may be insufficient. In the case of a true biological discontinuation effect or exposure misclassification, an attenuation of the primary estimate in the fixed-time model compared with the time-varying model would be expected. We found no evidence of this, but our study was underpowered to test the effect of statin discontinuation. However, the consistent small decrease in keratinocyte carcinoma risk associated with statin use in these models may reflect residual confounding, which is better controlled in the propensity score–matched analysis.

The VATTC study participants were at high risk for keratinocyte carcinoma. The incidence of keratinocyte carcinoma varies by sex and geographic region (56). The rates among the unexposed participants in this study were 50 to 100 times greater than those observed in the

general population (56). Whether our findings are generalizable to populations at low or moderate risk is unknown. We found the expected association between well-known risk factors and the occurrence of keratinocyte carcinoma, including male sex, older age, and sun sensitivity (data not shown) (30, 32).

Confounding by indication is an unlikely noncausal explanation of our estimates because risk factors for keratinocyte carcinoma are unlikely to influence the decision to prescribe statins, but we cannot rule out the possibility of unmeasured confounding. However, the VATTC investigators collected measurements on many potential confounders. This ascertainment of potential confounding factors is a strength of the study. Conducting the study in this setting was preferable to using data from cardiovascular disease prevention studies. There was little material confounding in our study, including among variables that we considered plausibly associated with statin use (for example, health behaviors, such as sunscreen use). This provides further evidence that unmeasured confounding is not at play. The estimated association between the use of other cholesterol-lowering drugs and keratinocyte carcinoma was compatible with chance despite a point estimate that suggests a protective effect. The implication of this finding is unclear, but it does not refute the hypothesis that statins may prevent cancer independently of cholesterol synthesis (20, 21). Previous work has shown that statin users are generally healthier than similarly aged nonusers (57). The rate ratios for other preventive therapies (for example, antihypertensives and other cholesterol-lowering agents) and keratinocyte carcinoma were close to 1.0, which suggests that the “healthy-user” effect does not explain our Cox regression findings.

Statins are prevalent, are well tolerated, and have been shown to improve outcomes for persons with cardiovascular disease. Preclinical research has elucidated potential mechanisms of a chemopreventive effect of statins, including beneficial effects on apoptosis and angiogenesis (20, 21). This study provides inconclusive evidence on the potential protective effect of statin use on the occurrence of cancer. Future studies must test the effect of individual statins on other types of cancer and assess whether this association varies by type of statin, dose, and duration of use.

Acknowledgments

The authors thank Kimberly Marcolivio, MEd; Robert Dyer, MD, MPH; and Margaret M. Boyle for their thoughtful assistance. They also acknowledge members of the VATTC trial group: study chairman Martin A. Weinstock, MD, PhD; Executive Committee members Martin A. Weinstock, MD, PhD, Russell P. Hall, MD, Mark F. Naylor, MD, Julia E. Vertrees, PharmD, John J. DiGiovanna, MD, and Stephen F. Bingham, PhD; study dermatopathologists Clifford R. White, Jr., MD, and Michael Piepkorn, MD; site investigators Russell P. Hall, MD, Mark F. Naylor, MD, David Eilers, MD, Jonette E. Keri, MD, James Kalivas, MD, Gary W. Cole, MD, Catherine Yanna, PA-C, and Robert S. Kirsner, MD; and study coordinator Kimberly Marcolivio, MEd.

Grant Support: Dr. Weinstock was supported by the Department of Veterans Affairs Office of Research and Development (CSP 402), and Dr. Dore was supported by the Agency for Healthcare Research and Quality (grant 5T32HS000011-21). Additional support was received from the American Cancer Society. Dr. Weinstock also received support from the National Institutes of Health (grants R01CA106592, R01CA106807, R25CA087972, and R01AR49342).

References

1. American Cancer Society. Cancer Facts & Figures. Atlanta: American Cancer Soc; 2006.
2. Miller DL, Weinstock MA. Nonmelanoma skin cancer in the United States: incidence. *J Am Acad Dermatol*. 1994; 30:774–778. [PMID: 8176018]. [PubMed: 8176018]
3. Weinstock MA. Nonmelanoma skin cancer mortality in the United States, 1969 through 1988. *Arch Dermatol*. 1993; 129:1286–1290. [PMID: 8215493]. [PubMed: 8215493]

4. Lewis KG, Weinstock MA. Trends in nonmelanoma skin cancer mortality rates in the United States, 1969 through 2000. *J Invest Dermatol.* 2007; 127:2323–2327. [PMID: 17522705]. [PubMed: 17522705]
5. Weinstock MA, Bogaars HA, Ashley M, Litle V, Bilodeau E, Kimmel S. Nonmelanoma skin cancer mortality A population-based study. *Arch Dermatol.* 1991; 127:1194–1197. [PMID: 1863078]. [PubMed: 1863078]
6. Green A, Williams G, Neale R, Hart V, Leslie D, Parsons P, et al. Daily sunscreen application and betacarotene supplementation in prevention of basal-cell and squamous-cell carcinomas of the skin: a randomised controlled trial. *Lancet.* 1999; 354:723–729. [PMID: 10475183]. [PubMed: 10475183]
7. Amarenco P, Bogousslavsky J, Callahan A3rd, Goldstein LB, Hennerici M, Rudolph AE, et al. Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Investigators High-dose atorvastatin after stroke or transient ischemic attack. *N Engl J Med.* 2006; 355:549–559. [PMID: 16899775]. [PubMed: 16899775]
8. Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, Beere PA, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS Air Force/Texas Coronary Atherosclerosis Prevention Study. *JAMA.* 1998; 279:1615–1622. [PMID: 9613910]. [PubMed: 9613910]
9. LaRosa JC, Grundy SM, Waters DD, Shear C, Barter P, Fruchart JC, et al. Treating to New Targets (TNT) Investigators Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med.* 2005; 352:1425–1435. [PMID: 15755765]. [PubMed: 15755765]
10. Mozaffarian D, Nye R, Levy WC. Statin therapy is associated with lower mortality among patients with severe heart failure. *Am J Cardiol.* 2004; 93:1124–1129. [PMID: 15110204]. [PubMed: 15110204]
11. Pedersen TR, Faergeman O, Kastelein JJ, Olsson AG, Tikkanen MJ, Holme I, et al. Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) Study Group High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial. *JAMA.* 2005; 294:2437–2445. [PMID: 16287954]. [PubMed: 16287954]
12. Etminan M, Gill S, Samii A. The role of lipid-lowering drugs in cognitive function: a meta-analysis of observational studies. *Pharmacotherapy.* 2003; 23:726–730. [PMID: 12820814]. [PubMed: 12820814]
13. Zhou B, Teramukai S, Fukushima M. Prevention and treatment of dementia or Alzheimer's disease by statins: a meta-analysis. *Dement Geriatr Cogn Disord.* 2007; 23:194–201. [PMID: 17259710]. [PubMed: 17259710]
14. Bauer DC, Mundy GR, Jamal SA, Black DM, Cauley JA, Ensrud KE, et al. Use of statins and fracture: results of 4 prospective studies and cumulative meta-analysis of observational studies and controlled trials. *Arch Intern Med.* 2004; 164:146–152. [PMID: 14744837]. [PubMed: 14744837]
15. Wang PS, Solomon DH, Mogun H, Avorn J. HMG-CoA reductase inhibitors and the risk of hip fractures in elderly patients. *JAMA.* 2000; 283:3211–3216. [PMID: 10866868]. [PubMed: 10866868]
16. Neuhaus O, Stüve O, Zamvil SS, Hartung HP. Are statins a treatment option for multiple sclerosis? *Lancet Neurol.* 2004; 3:369–371. [PMID: 15157852]. [PubMed: 15157852]
17. Vollmer T, Key L, Durkalski V, Tyor W, Corboy J, Markovic-Plese S, et al. Oral simvastatin treatment in relapsing-remitting multiple sclerosis. *Lancet.* 2004; 363:1607–1068. [PMID: 15145635]. [PubMed: 15145635]
18. Friis S, Poulsen AH, Johnsen SP, McLaughlin JK, Fryzek JP, Dalton SO, et al. Cancer risk among statin users: a population-based cohort study. *Int J Cancer.* 2005; 114:643–647. [PMID: 15578694]. [PubMed: 15578694]
19. Poynter JN, Gruber SB, Higgins PD, Almog R, Bonner JD, Rennert HS, et al. Statins and the risk of colorectal cancer. *N Engl J Med.* 2005; 352:2184–2192. [PMID: 15917383]. [PubMed: 15917383]

20. Dulak J, Józkowicz A. Anti-angiogenic and anti-inflammatory effects of statins: relevance to anti-cancer therapy. *Curr Cancer Drug Targets*. 2005; 5:579–594. [PMID: 16375664]. [PubMed: 16375664]
21. Hindler K, Cleeland CS, Rivera E, Collard CD. The role of statins in cancer therapy. *Oncologist*. 2006; 11:306–315. [PMID: 16549815]. [PubMed: 16549815]
22. Hoque A, Chen H, Xu XC. Statin induces apoptosis and cell growth arrest in prostate cancer cells. *Cancer Epidemiol Biomarkers Prev*. 2008; 17:88–94. [PMID: 18199714]. [PubMed: 18199714]
23. Ogunwobi OO, Beales IL. Statins inhibit proliferation and induce apoptosis in Barrett's esophageal adenocarcinoma cells. *Am J Gastroenterol*. 2008; 103:825–837. [PMID: 18371146]. [PubMed: 18371146]
24. Coogan PF, Rosenberg L, Strom BL. Statin use and the risk of 10 cancers. *Epidemiology*. 2007; 18:213–219. [PMID: 17235211]. [PubMed: 17235211]
25. Blais L, Desgagné A, LeLorier J. 3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors and the risk of cancer: a nested case-control study. *Arch Intern Med*. 2000; 160:2363–2368. [PMID: 10927735]. [PubMed: 10927735]
26. Karp I, Behloul H, Leloir J, Pilote L. Statins and cancer risk. *Am J Med*. 2008; 121:302–309. [PMID: 18374689]. [PubMed: 18374689]
27. Jagdeo J, Weinstock MA, Piepkorn M, Bingham SF. Department of Veteran Affairs Topical Tretinoin Chemoprevention Trial Group Reliability of the histopathologic diagnosis of keratinocyte carcinomas. *J Am Acad Dermatol*. 2007; 57:279–284. [PMID: 17482716]. [PubMed: 17482716]
28. Weinstock MA, Bingham SF, Cole GW, Eilers D, Naylor MF, Kalivas J, et al. keratoses Reliability of counting actinic before and after brief consensus discussion: the VA topical tretinoin chemoprevention (VATTC) trial. *Arch Dermatol*. 2001; 137:1055–1058. [PMID: 11493098]. [PubMed: 11493098]
29. Smith MW, Joseph GJ. Pharmacy data in the VA health care system. *Med Care Res Rev*. 2003; 60:92S–123S. [PMID: 15095548]. [PubMed: 15095548]
30. Gallagher RP, Hill GB, Bajdik CD, Coldman AJ, Fincham S, McLean DI, et al. Sunlight exposure pigmentation factors risk of nonmelanocytic skin cancer II. Squamous cell carcinoma. *Arch Dermatol*. 1995; 131:164–169. [PMID: 7857112]. [PubMed: 7857112]
31. Kricke A, Armstrong BK, English DR, Heenan PJ. Does intermittent sun exposure cause basal cell carcinoma? A case-control study in Western Australia. *Int J Cancer*. 1995; 60:489–494. [PMID: 7829262]. [PubMed: 7829262]
32. Lear JT, Tan BB, Smith AG, Bowers W, Jones PW, Heagerty AH, et al. Risk factors for basal cell carcinoma in the UK: case-control study in 806 patients. *J R Soc Med*. 1997; 90:371–374. [PMID: 9290417]. [PubMed: 9290417]
33. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987; 40:373–383. [PMID: 3558716]. [PubMed: 3558716]
34. Romano PS, Roos LL, Jollis JG. Adapting a clinical comorbidity index for use with ICD-9-CM administrative data: differing perspective. *J Clin Epidemiol*. 1993; 46:1075–1079. discussion 1081–90. [PMID: 8410092]. [PubMed: 8410092]
35. Fortina AB, Piaserico S, Caforio AL, Abeni D, Alaibac M, Angelini A, et al. Immunosuppressive level and other risk factors for basal cell carcinoma and squamous cell carcinoma in heart transplant recipients. *Arch Dermatol*. 2004; 140:1079–1085. [PMID: 15381547]. [PubMed: 15381547]
36. Grau MV, Baron JA, Langholz B, Karagas M, Greenberg ER, Stukel TA, et al. Effect of NSAIDs on the recurrence of nonmelanoma skin cancer. *Int J Cancer*. 2006; 119:682–686. [PMID: 16496410]. [PubMed: 16496410]
37. Seeger JD, Williams PL, Walker AM. An application of propensity score matching using claims data. *Pharmacoepidemiol Drug Saf*. 2005; 14:465–476. [PMID: 15651087]. [PubMed: 15651087]
38. Brookhart MA, Schneeweiss S, Rothman KJ, Glynn RJ, Avorn J, Stürmer T. Variable selection for propensity score models. *Am J Epidemiol*. 2006; 163:1149–1156. [PMID: 16624967]. [PubMed: 16624967]

39. Parsons, L. Reducing bias in a propensity score matched-pair sample using greedy matching techniques; Long Beach, California. Proceedings of the 26th Annual SAS Users Group International Conference; 22–25 April 2001; Cary, NC: SAS Institute; 2001. p. 214–226.
40. Stein EA, Corsini A, Gimpelewicz CR, Bortolini M, Gil M. Fluvastatin treatment is not associated with an increased incidence of cancer. *Int J Clin Pract*. 2006; 60:1028–1034. [PMID: 16939542]. [PubMed: 16939542]
41. Dellavalle RP, Drake A, Graber M, Heilig LF, Hester EJ, Johnson KR, et al. Statins and fibrates for preventing melanoma. *Cochrane Database Syst Rev*. 2005 CD003697. [PMID: 16235336].
42. Boudreau DM, Yu O, Buist DS, Miglioretti DL. Statin use and prostate cancer risk in a large population-based setting. *Cancer Causes Control*. 2008; 19:767–774. [PMID: 18322813]. [PubMed: 18322813]
43. Flick ED, Habel LA, Chan KA, Van Den Eeden SK, Quinn VP, Haque R, et al. Statin use and risk of prostate cancer in the California Men's Health Study cohort. *Cancer Epidemiol Biomarkers Prev*. 2007; 16:2218–2225. [PMID: 17971519]. [PubMed: 17971519]
44. Murtola TJ, Tammela TL, Lahtela J, Auvinen A. Cholesterol-lowering drugs and prostate cancer risk: a population-based case-control study. *Cancer Epidemiol Biomarkers Prev*. 2007; 16:2226–2232. [PMID: 18006910]. [PubMed: 18006910]
45. Platz EA, Leitzmann MF, Visvanathan K, Rimm EB, Stampfer MJ, Willett WC, et al. Statin drugs and risk of advanced prostate cancer. *J Natl Cancer Inst*. 2006; 98:1819–1825. [PMID: 17179483]. [PubMed: 17179483]
46. Coogan PF, Smith J, Rosenberg L. Statin use and risk of colorectal cancer. *J Natl Cancer Inst*. 2007; 99:32–40. [PMID: 17202111]. [PubMed: 17202111]
47. Vinogradova Y, Hippisley-Cox J, Coupland C, Logan RF. Risk of colorectal cancer in patients prescribed statins, nonsteroidal anti-inflammatory drugs, and cyclooxygenase-2 inhibitors: nested case-control study. *Gastroenterology*. 2007; 133:393–402. [PMID: 17681160]. [PubMed: 17681160]
48. Farwell WR, Scranton RE, Lawler EV, Lew RA, Brophy MT, Fiore LD, et al. The association between statins and cancer incidence in a veterans population. *J Natl Cancer Inst*. 2008; 100:134–139. [PMID: 18182618]. [PubMed: 18182618]
49. Khurana V, Caldito G, Ankem M. Statins might reduce risk of renal cell carcinoma in humans: case-control study of 500,000 veterans. *Urology*. 2008; 71:118–122. [PMID: 18242378]. [PubMed: 18242378]
50. Setoguchi S, Glynn RJ, Avorn J, Mogun H, Schneeweiss S. Statins and the risk of lung, breast, and colorectal cancer in the elderly. *Circulation*. 2007; 115:27–33. [PMID: 17179016]. [PubMed: 17179016]
51. Dale KM, Coleman CI, Henyan NN, Kluger J, White CM. Statins and cancer risk: a meta-analysis. *JAMA*. 2006; 295:74–80. [PMID: 16391219]. [PubMed: 16391219]
52. Salinas CA, Agalliu I, Stanford JL, Lin DW. Statins and the risk of cancer [Letter]. *JAMA*. 2006; 295:272–271. author reply 2721–2. [PMID: 16788124].
53. Freeman MR, Solomon KR, Moyad M. Statins and the risk of cancer [Letter]. *JAMA*. 2006; 295:2720–2721. author reply 2721–2. [PMID: 16788122]. [PubMed: 16788122]
54. Salinas CA, Agalliu I, Stanford JL, Lin DW. Statins and the risk of cancer [Letter]. *JAMA*. 2006; 295 author reply 2721–2. [PMID: 16788124].
55. Sloan KL, Sales AE, Liu CF, Fishman P, Nichol P, Suzuki NT, et al. Construction and characteristics of the RxRisk-V: a VA-adapted pharmacy-based case-mix instrument. *Med Care*. 2003; 41:761–774. [PMID: 12773842]. [PubMed: 12773842]
56. Karagas, M.; Weinstock, M.; Nelson, H. Keratinocyte carcinomas (basal and squamous cell carcinomas of the skin). In: Schottenfeld, D.; Fraumeni, JF., editors. *Cancer Epidemiology Prevention*. 3rd ed.. New York: Oxford Univ Pr; 2006. p. 1230–1250.
57. Mehta JL, Bursac Z, Hauer-Jensen M, Fort C, Fink LM. Comparison of mortality rates in statin users versus nonstatin users in a United States veteran population. *Am J Cardiol*. 2006; 98:923–928. [PMID: 16996875]. [PubMed: 16996875]

Appendix

Appendix Table

Reliability of Diagnoses of Keratinocyte Carcinoma Between Reference Dermatopathologists Among a 10% Random Sample in the Veterans Affairs Topical Tretinoin Chemoprevention Trial

Variable	Dermatopathologist 2	
	Positive	Negative
Keratinocyte carcinoma <i>n</i> (%)		
Dermatopathologist 1		
Positive	167 (47.0)	43 (12.1)
Negative	17 (4.8)	128 (36.1)
Basal cell carcinoma <i>n</i> (%)		
Dermatopathologist 1		
Positive	116 (32.7)	3 (0.8)
Negative	17 (4.8)	219 (61.7)
Invasive squamous cell carcinoma <i>n</i> (%)		
Dermatopathologist 1		
Positive	51 (14.4)	40 (11.3)
Negative	0 (0)	264 (74.4)

Context

Statins are pharmacologically pleiotropic. Some studies suggest that these agents may prevent keratinocyte carcinoma.

Contribution

In this analysis of data from a Veterans Affairs trial of topical tretinoin for prevention of skin cancer, 37% of 1037 participants at high risk for keratinocyte carcinoma were taking statins. During a median follow-up of 3.5 years, half of the participants had keratinocyte carcinoma. Analyses showed no statistically significant associations between statin use and risk for keratinocyte carcinoma.

Caution

Confidence bounds around the measures of associations were wide.

Implication

Evidence that statins prevent keratinocyte carcinoma is inconclusive.

Figure 1.
Study flow diagram.
VATTC = Veterans Affairs Topical Tretinoin Chemoprevention.
*Includes 98 statin users and 331 nonusers.

Persons at Risk, n

Exposed

397 357 297 243 211 168 133 83 59 38 26 15

Unexposed

640 552 452 371 301 223 173 108 84 61 41 17

Figure 2.

Crude cumulative incidence of keratinocyte carcinoma among statin users and nonusers in the Veterans Affairs Topical Tretinoin Chemoprevention Trial.

Table 1**Exclusion Criteria in the Veterans Affairs Topical Tretinoin Chemoprevention Trial**

Use of systemic retinoid or cytotoxic therapy in the previous 6 months
History of noncutaneous invasive cancer
History of metastatic cutaneous cancer
Other severe or end-stage disease (e.g., cardiovascular diseases)
Known allergy to tretinoin or its vehicle ingredients
Xeroderma pigmentosum
The basal cell nevus syndrome
History of major organ transplantation
Known arsenic exposure
Psoralen + UVA photochemotherapy
Mycosis fungoides
Pregnant or breastfeeding
Previous or current radiation therapy of the face, ears, or area of previous keratinocyte carcinoma
Probable difficulty in adhering to study protocols

UVA = ultraviolet A.

Table 2
Characteristics of Statin Users and Nonusers in the Veterans Affairs Topical Retinoin Chemoprevention Trial

Variable	Full Cohort		Propensity Score-Matched Cohort	
	Statin Users (n = 397)	Nonusers (n = 640)	Statin Users (n = 304)	Nonusers (n = 304)
			P Value*	P Value*
Demographic characteristics				
Age, n (%)				
<60 y	37 (9.3)	97 (15.2)	-	31 (10.2)
60–69 y	105 (26.5)	170 (26.6)	-	82 (27.0)
70–79 y	192 (48.4)	262 (40.9)	-	142 (46.7)
80 y	63 (15.9)	111 (17.3)	0.02	49 (16.1)
Men, n (%)	385 (97.0)	621 (97.0)	0.96	298 (98.0)
Non-Hispanic white, n (%)	395 (99.5)	630 (98.4)	0.12	303 (99.7)
Education, n (%)				
Less than high school	71 (18.1)	140 (21.9)	-	58 (19.1)
High school diploma	101 (25.4)	125 (19.5)	-	80 (26.3)
At least some college	217 (54.7)	363 (56.7)	0.12	164 (53.6)
Marital status, n (%)	241 (61.8)	379 (60.3)	-	181 (59.7)
Married				
Single	37 (9.5)	69 (11.0)	-	31 (10.3)
Widowed, divorced, or separated	112 (28.7)	181 (28.7)	0.96	90 (29.8)
Keratinocyte carcinoma risk factors				
Mean intrinsic sun-sensitivity score (SD) [†]	0.56 (0.19)	0.64 (0.19)	0.27	0.56 (0.19)
>3 actinic keratoses, n (%)	179 (45.1)	309 (48.3)	0.32	138 (45.4)

Variable	Full Cohort		Propensity Score–Matched Cohort			
	Statin Users (<i>n</i> = 397)	Nonusers (<i>n</i> = 640)	<i>P</i> Value*	Statin Users (<i>n</i> = 304)	Nonusers (<i>n</i> = 304)	<i>P</i> Value*
Ever smoked cigarettes, <i>n</i> (%)	293 (74.7)	454 (72.2)	0.36	226 (74.3)	223 (73.4)	0.78
Ever used tanning bed for nonmedical purpose, <i>n</i> (%)	33 (8.4)	65 (10.3)	0.32	26 (8.5)	28 (9.2)	0.78
Ever used 5-fluorouracil, <i>n</i> (%)	72 (18.4)	128 (20.4)	0.44	58 (19.1)	54 (17.8)	0.68
Eczema, <i>n</i> (%)	11 (2.8)	34 (5.4)	0.05	10 (3.3)	10 (3.3)	1.0
Psoriasis, <i>n</i> (%)	22 (5.6)	29 (4.6)	0.47	15 (4.9)	12 (3.4)	0.56
Blood relative with skin cancer, <i>n</i> (%)	102 (26.8)	174 (28.6)	0.55	83 (28.3)	79 (26.9)	0.69
Previous sun exposure						
Mean number of days outdoors >2 h in past 6 mo (SD) [†]	62.7 (75.6)	60.8 (73.7)	0.68	65.0 (75.6)	59.3 (72.3)	0.35
Sunburn in past 5 y that caused pain for 2 d, <i>n</i> (%)	11 (2.8)	32 (5.1)	0.08	11 (3.6)	8 (2.6)	0.48
Sunburn from age 12–17 y that caused pain for 2 d, <i>n</i> (%)	156 (40.3)	267 (42.7)	0.34	115 (37.8)	117 (38.5)	0.87
Spent >2 h/d outside from 10 a.m. to 3 p.m. for >15 d in past 6 mo, <i>n</i> (%)	196 (50.1)	315 (50.4)	0.93	159 (52.3)	152 (50.0)	0.57
Clinical characteristics [‡] <i>n</i> (%)						
Inflammatory acne	72 (18.1)	153 (23.9)	0.16	59 (19.4)	70 (23.0)	0.50
Rhinophyma	80 (20.1)	193 (30.2)	0.01	66 (21.7)	70 (23.0)	0.81
Used a nonstatin cholesterol-lowering drug [‡]	79 (19.9)	48 (7.5)	<0.001	45 (14.8)	40 (13.2)	0.56
Used an immunosuppressant [‡]	72 (18.1)	150 (23.4)	0.04	62 (20.4)	53 (17.4)	0.35
Used an ACE inhibitor [‡]	270 (68.0)	320 (50.0)	<0.001	185 (60.9)	186 (61.2)	0.93
Used an NSAID [‡]	246 (62.0)	405 (63.3)	0.67	186 (61.2)	186 (61.2)	1.0
Randomly assigned to receive tretinoin	199 (50.1)	327 (51.1)	0.76	149 (49.0)	143 (47.0)	0.63

Variable	Full Cohort		Propensity Score–Matched Cohort	
	Statin Users (<i>n</i> = 397)	Nonusers (<i>n</i> = 640)	Statin Users (<i>n</i> = 304)	Nonusers (<i>n</i> = 304)
			<i>P</i> Value*	<i>P</i> Value*
Charlson Comorbidity Index score	113 (28.5)	246 (38.4)	-	-
0				
1–3	206 (51.9)	321 (50.2)	-	-
4	78 (19.7)	73 (11.4)	<0.001	0.94

ACE = angiotensin-converting enzyme; NSAID = nonsteroidal anti-inflammatory drug.

* Estimated by chi-square tests for categorical variables and 2-sample *t* tests for continuous variables.

† The intrinsic sun-sensitivity score is the numerical average of measures of hair color, propensity to sunburn, freckling, untanned skin color, post-sun exposure skin color, and presence of tan lines.

‡ Use of medications at any point from 29 September 1998 to study end.

Table 3

Distribution and Daily Dose of Statins in the Veterans Affairs Topical Tretinoin Chemoprevention Trial (Full Cohort)

Drug	Randomization n (%)	End of Follow-up n (%)
Simvastatin	287 (72.3)	294 (74.1)
Lovastatin	101 (25.4)	84 (21.2)
Atorvastatin	7 (1.8)	17 (4.3)
Pravastatin	2 (0.5)	2 (0.5)
Daily dose *		
<20 mg	143 (36.0)	87 (21.9)
20–39 mg	145 (36.5)	122 (30.7)
40–59 mg	87 (21.9)	115 (29.0)
60 mg	15 (3.8)	61 (15.4)

* All statins are assumed to be equipotent.

Relation Between Statin Exposure at Randomization and the Incidence of Keratinocyte Carcinoma in the Veterans Affairs Topical Tretinoin Chemoprevention Trial (Full and Propensity Score-Matched Cohorts)

Table 4

Cohort	Statin Users			Nonusers			Crude Rate Ratio (95% CI)	Adjusted Rate Ratio (95%CI)*
	Cases <i>n</i>	Follow-up <i>person-years</i>	Rate per 1000 Person-Years	Cases <i>n</i>	Follow-up <i>person-years</i>	Rate per 1000 Person-Years		
Full cohort (<i>n</i> = 1037)								
All KC	192	924.7	207.6	347	1371.1	253.1	0.83 (0.69–0.98)	0.84 (0.70–1.02)
BCC	158	1017.5	155.3	277	1571.6	176.3	0.88 (0.72–1.07)	0.91 (0.73–1.12)
SCC	83	1302.5	63.7	168	1902.1	88.3	0.78 (0.60–1.02)	0.86 (0.65–1.15)
Propensity score-matched cohort (<i>n</i> = 608) [†]								
All KC	145	716.6	202.3	150	683.6	219.4	-	0.92 (0.73–1.16)
BCC	117	789.6	148.2	118	762.6	154.7	-	0.96 (0.74–1.24)
SCC	64	915.1	69.9	73	915.5	79.7	-	0.88 (0.63–1.23)

BCC = basal cell carcinoma; KC = keratinocyte carcinoma; SCC = squamous cell carcinoma.

* Adjusted for age; sex; Charlson Comorbidity Index score; cigarette smoking; intrinsic sun sensitivity; number of actinic keratoses; skin oiliness; use of other cholesterol-lowering medications; sunscreen use; sun exposure; sunburns during childhood, adolescence, and adulthood; and study center. Propensity score-matched estimates are adjusted for the same variables as the Cox regression estimates and cumulative photodamage; psoriasis; eczema; dermatitis; and use of tanning beds, therapeutic ultraviolet therapy, chemical peels, 5-fluorouracil, angiotensin-converting enzyme inhibitors, immunosuppressants, and nonsteroidal anti-inflammatory drugs.

[†] 98 statin users could not be matched to nonusers.