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Statin Use and Risk of Skin Cancer

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Abstract

Background—Statins are among the most commonly used medications in the United States, and statin use is associated with increased risk of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). However, previous studies are limited by lack of adjustment for important confounders.

Objective—Examine the relation between statins and skin cancer risk in the Nurses' Health Study and Health Professionals Follow-up Study.

Methods—Cox proportional hazards regression was used to evaluate associations.

Results—During follow-up (2000–2010), we documented 10,201 BCC, 1,393 SCC, and 333 melanoma cases. History of high cholesterol was not associated with risk of BCC (pooled

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multivariable-adjusted Hazard ratio (HR)=1.04 [1.00, 1.09], SCC (HR=0.95 [0.85, 1.06]), or melanoma (HR=0.87 [0.64, 1.19]). Statin use was not associated with risk of BCC (HR=1.04 [0.99, 1.09]), SCC (HR=1.08 [0.94, 1.24]), or melanoma (HR=1.04 [0.78, 1.38]). There was a trend towards higher BCC risk with longer duration of statin use in men (*P-trend*=0.003), but not in women (*P-trend*=0.86).

Limitations—Lack of treatment data.

Conclusion—History of high cholesterol was not associated with skin cancer risk. Longer duration of statin use was associated with a trend towards higher BCC risk in men.

Keywords

Statins; basal cell carcinoma; squamous cell carcinoma; melanoma

INTRODUCTION

The incidence of melanoma and keratinocyte carcinomas (KCs) – which are comprised of squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) of the skin – have been increasing in the United States and worldwide, and represent a significant economic burden.[1–5]

High cholesterol is also common and affects approximately 13% of adults in the United States.[6] Several cellular mechanisms that promote altered cholesterol homeostasis have been associated with cancer development,[7–12] and high cholesterol has been associated with increased risk of certain malignancies including prostate cancer.[13, 14] However, the potential relation between high cholesterol, KCs, and melanoma has not been previously investigated.

Recent estimates from the National Health and Nutrition Examination Survey (NHANES) suggest that 17% of adults in the United States are on a statin medication.[15] In contrast to the lack of studies on the potential relation between skin cancers and high cholesterol, there has been some investigation of the relation between skin cancers and statin (3-hydroxy-3 methylglutaryl coenzyme A inhibitors) use.

Although primarily prescribed as cholesterol-lowering medications, statins have been shown to have pleiotropic properties, which include inhibition of tumor cell growth.[16–19] Conversely, statins have also been associated immunosuppression and inhibition of the Ras signaling pathway,[20–23] which has been associated with development of KCs.[24–26] A large prospective study in women demonstrated no significant association between statin use and risk of melanoma.[27] Previous studies investigating the relation between statin use and KCs found an increased risk of KCs with statin use.[28–31] However, data from these studies are limited by lack of adjustment for UV light exposure[28] and lack of malignancy verification and diagnosis date.[29]

We prospectively investigated the relation between high cholesterol, statin use and risk of melanoma, SCC, and BCC in the Nurses' Health Study (NHS) and the Health Professionals Follow-up Study (HPFS) – two cohorts followed by our research group.

MATERIALS AND METHODS

Study participants

The Nurses' Health Study (NHS) is a prospective cohort of 121,700 registered female nurses aged 30–55 years at study onset in 1976. The Health Professionals' Follow-up Study (HPFS) was established when 51,529 male health professionals aged 40–75 years were enrolled in 1986. In both cohorts, follow-up questionnaires are administered biennially, with an average follow-up rate of greater than 90% of the eligible person-time. This study was approved by the Partners Healthcare Institutional Review Board (1999P011114).

Ascertainment of high cholesterol

On the 1976 and 1978 NHS questionnaires, participants were asked whether they had elevated cholesterol. On the 1980 NHS questionnaire and 1986 HPFS questionnaire, and every two years thereafter, participants were asked whether a clinician had diagnosed them as having elevated cholesterol. We classified participants who answered, "yes" to this question as having a history of high cholesterol from that time onwards. A previous validation study in NHS demonstrated self-reported cases of elevated cholesterol levels are highly reliable, with greater than 85% of reported cases confirmed via review of medical records.[32]

Ascertainment of medication use

In 2000, and every two years thereafter, NHS and HPFS participants were asked whether they regularly used statins. We considered women who answered "yes" to have taken the statins for the previous two years. Participants were also asked in 2000 the number of years they used "Statin cholesterol-lowering drugs" prior to the 2000 questionnaire cycle.

Identification of skin cancer cases

Cohort participants reported new cases of skin cancer biennially. Study physicians reviewed participant medical and pathology reports to verify cases of SCC and melanoma. Although medical records were not obtained for cases of reported BCC, previous validation studies performed in these cohorts have demonstrated approximately 90% accuracy in self-reported BCC cases, when confirmed by pathology or medical records.[32, 33]

Ascertainment of covariates

Covariates were selected based on previously reported related factors for melanoma and KCs.[34] Factors considered included age, natural hair color, number of skin moles, cumulative ultraviolet flux, skin reaction to prolonged sun exposure during childhood/adolescence, number of lifetime severe or blistering sunburns, family history of melanoma, smoking status, body mass index, citrus consumption,[35, 36] and physical activity. Data on covariates were obtained from the biennial questionnaires. Dietary factors were derived from semiquantitative food frequency questionnaires mailed to participants every four years. Physical activity was derived from questionnaire information obtained every four years in NHS, and every two years in HPFS. Time-dependent covariates were updated with each

questionnaire cycle, when available. In cases where covariate information was missing, information from the previous questionnaire cycle was carried forward.

Statistical analysis

All analyses were performed in a prospective manner using information on high cholesterol and medication use that was collected before the reported case of melanoma or KC. We considered participants who reported high cholesterol in or prior to 2000 (the baseline year of our study) as having a history of high cholesterol. If on a subsequent questionnaire, participants reported having high cholesterol, they were considered to have a history of high cholesterol from that point onward. Duration of statin use was derived by taking the number of years participants reported using statins prior to the 2000 questionnaire cycle, and assigning two additional years of statin use for participants who reported use of statins in any given two-year time period over the follow-up period. Duration of statin use was categorized as <1 year, 1–2 years, 3–4 years, 5–6 years, 7–8 years, and >8 years of statin use in our SCC and BCC analyses, and <1 year, 1–2 years, 3–4 years, >4 years of statin use in our melanoma analyses. A *P-trend* was utilized to test for an overall trend towards significance by increasing categorical duration of statin use.

Multivariable-adjusted relative risks were calculated using Cox proportional hazards regression models. We examined the relation between high cholesterol, statin use, and skin cancer by first examining the relation between history of high cholesterol and skin cancer and subsequently limiting our analysis on statin use and risk of skin cancer to participants with a history of high cholesterol. We performed a separate analysis investigating high cholesterol, statin use, and risk of melanoma that did not exclude participants with a history of SCC or BCC at baseline, and instead adjusted for a history of SCC or history of BCC in the statistical model. We also ran separate models that included adjustment for use of oral steroid medications. We also performed a secondary analysis to evaluate whether the relation between high serum cholesterol, statin use, and risk of skin cancers varied by health screening among participants. Participants were asked each questionnaire cycle whether they underwent a physical examination over the past two years, and we accounted for their responses in our multivariable models. All p-values are two-sided, with 95% confidence intervals calculated for all relative risks. SAS software, version 9.4 (SAS Institute Inc., Cary, North Carolina) was used to perform all statistical analyses.

RESULTS

Participant characteristics at baseline according to history of high cholesterol and statin use are shown in Table 1. At baseline, 34,376 women (60.0%) and 10,590 men (50.3%) reported a history of high cholesterol. Among participants who reported a history of high cholesterol, 11,743 women (34.2%) and 4,341 men (41.0%) reported statin use.

During the ten-year follow-up period (2000–2010), 10,201 incident cases of BCC, 1,393 incident cases of SCC, and 333 incident cases of melanoma were identified. History of high cholesterol was not associated with risk of BCC (multivariable adjusted relative risk (MVRR) = 1.03; 95% confidence interval (CI) = 0.98, 1.08), SCC (MVRR = 0.94; 95% CI = 0.82, 1.08), or melanoma (MVRR = 0.77; 95% CI = 0.58, 1.01) among women (Table 2).

Among men, history of high cholesterol was not associated with risk of any skin cancer; the HR [95% CI] was 1.08 [1.00, 1.16] for BCC, 0.97 [0.81, 1.16] for SCC, and 1.06 [0.71, 1.57] for melanoma.

Among participants with a history of high cholesterol, we did not find significant associations between statin use and risk of BCC, SCC, or melanoma in either women or men (Table 3). In a pooled analysis of the cohorts, the HR [95% CI] was 1.04 [0.99, 1.09] for BCC, 1.08 [0.94, 1.24] for SCC, and 1.04 [0.78, 1.38] for melanoma.

Duration of statin use was not associated with risk of BCC (*P-trend* = 0.86), SCC (*P-trend* = 0.89), or melanoma (*P-trend* = 0.68) among women (Table 4). Longer duration of statin use was associated with increased risk of BCC (*P-trend* = 0.003) among men. Men who reported statin use for 3–4 years, 5–6 years, and >8 years had an approximately 7%, 12%, and 28% higher risk of BCC, respectively, compared with men who reported <1 year of statin use. Duration of statin use was not associated with risk of SCC (*P-trend* = 0.09) or melanoma among men (*P-trend* = 0.80). In a pooled analysis of the cohorts, longer duration of statin use was not associated with risk of BCC (*P-trend* = 0.20), SCC (*P-trend* = 0.28) or melanoma (*P-trend* = 0.68).

An analysis of type of statin use and risk of BCC, SCC, and melanoma (Table 5) demonstrated lower risk of BCC with pravastatin use compared with no statin use in men (MVRR = 0.62; 95% CI = 0.41, 0.93) and a lower risk of BCC with pravastatin use compared with no statin use in men and women combined (MVRR = 0.88; 95% CI = 0.79, 0.99). There was a higher risk of SCC with lovastatin use compared with no statin use in women (MVRR = 1.82; 95% CI = 1.15, 2.88), and a higher risk of SCC with lovastatin use compared with no statin use in men and women combined (MVRR = 1.77; 95% CI = 1.20, 2.63).

A secondary analysis for melanoma was conducted without excluding participants having a history of BCC or SCC at baseline, but instead adjusting for history of BCC and SCC, and did not materially change the results. Accounting for oral steroid use did not materially change our results. Accounting for health screening among participants did not change our results either (data not shown).

DISCUSSION

History of high cholesterol was not associated with risk of BCC or SCC in women and men. Statin use among participants with a history of high cholesterol was not associated with risk of SCC, BCC, or melanoma, but there was a significant trend towards higher risk of BCC with longer duration of statin use in men.

High cholesterol has been associated with increased risk of developing some cancers including prostate cancer.[13, 14] Cellular mechanisms associated with impaired cholesterol homeostasis have been associated with higher risk of cancer. Inhibition of the ABCA1 gene – which in normal cells mediates transfer of cholesterol across the plasma membrane – has been associated with increased mitochondrial cholesterol, which inhibits the release of mitochondrial apoptosis-promoting molecules, thus facilitating cancer cell survival.[7] Our

data shows no association between high cholesterol and risk of BCC, SCC, or melanoma in HPFS and NHS.

Previous studies present conflicting evidence with regards to the association between statin use and KC, reporting positive,[28–31] negative,[37–39] or no associations.[40–43] A recent large epidemiological study in the Women's Health Initiative demonstrated an increased risk of KC with statin use.[44] However, their data were limited by the self-reported nature of KCs, and lack of malignancy diagnosis date. Some studies suggest statin use may increase risk of KC due to increased regulatory T cells secondary to immunomodulation,[45–47] and statins have been associated with inhibition of the ras signaling pathway,[20–22] which has been associated with development of KCs.[24–26] There is increasing evidence that suggests a higher incidence of KCs among immunosuppressed individuals,[48] and thus, the potential immunosuppressive behavior of statins may serve to increase risk of KCs among statin users.[23] Conversely, statin-induced changes in other cellular pathways have been associated with decreased risk of KC.[16, 49–54] Our data showed no association between any statin use and risk of BCC, SCC, or melanoma. However, there was a significant trend towards higher risk of BCC with longer duration of statin use in men, but no association between risk of BCC with duration of statin use in women. This finding suggests that there may be differences between the physiological consequences of long-term statin exposure between men and women. Further, it suggests that the potential effects of statin use may be the result of cumulative, long-term exposure to statins.

Statins have been shown to have inhibitory effects on human melanoma cells secondary to inhibition of angiogenesis, cell growth,[18, 19, 55] and promoting apoptosis.[17, 56] A recent meta-analysis that included data from a number of randomized controlled trials and cohort studies demonstrated no association between statin use and risk of melanoma.[42] Further, a prospective study in postmenopausal women demonstrated no association between statin use and risk of melanoma.[27] In our study, there was no association between statin use or risk of melanoma in men or in women.

Different statins have been shown to have varying degrees of solubility in octanol (lipophilicity) and lipid-lowering potency.[57–60] A previous study examining the association between statin type and risk of keratinocyte carcinomas demonstrated higher odds of KC with lovastatin use and simvastatin use compared with no statin use in women, which the authors suggested may be related to varying lipophilicity and potency of these drugs.[29] In our study, we found a higher risk of SCC with lovastatin use compared with no statin use in men and women, which is consistent with the findings from the previous study. However, we found no association between risk of SCC or BCC with simvastatin use in our study, and a lower risk of BCC with pravastatin use compared with no statin use in men. These findings suggest the association between statin use and risk of BCC may differ by statin type.

Our study has limitations. History of high cholesterol and statin use was self-reported, and we lacked information on duration of statin use prior to the baseline year. Although we were able to determine duration of statin use, our study lacked information on statin dose in participants. However, data were prospectively collected over 10 years in this study, and information provided by these cohorts has been shown to be highly reliable in previous

studies.[32, 61–63] We adjusted for many potential confounders in our multivariable models, but given the relatively few cases of melanoma in our cohort, the interpretability of our melanoma analyses may be limited. However, it is worth nothing that our findings are consistent with results from a previous large prospective study on the relation between statin use and risk of melanoma.[27] We limited our analyses to white participants, given the small sample size and lack of skin cancer cases in other ethnicities.

In conclusion, history of high cholesterol was not associated with risk of keratinocyte carcinomas or melanoma, and longer duration of statin use may be associated with higher risk of basal cell carcinoma in men. Our data suggest there may be differences in the physiological consequences of long-term statin exposure and risk of skin cancers between men and women. Individuals using statins long-term may benefit from counseling on the importance of routine self-surveillance and health screening.

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ABBREVIATIONS

KCs	Keratinocyte carcinomas
SCC	Squamous cell carcinoma
BCC	Basal cell carcinoma
NHS	Nurses' Health Study
HPFS	Health Professionals Follow-up Study
MVRR	Multivariable adjusted relative risk

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Table 1

Baseline Characteristics of Participants According to History of High Cholesterol and Statin use in Women in the Nurses' Health Study (NHS) and in Men in the Health Professionals Follow-up Study (HPFS)

	History of High Cholesterol		Statin Use	
	No	Yes	No	Yes
Women in NHS (2000)				
No. of participants	22,862	34,376	45,119	12,119
Age, years [a]	64.1(7.1)	66.1(6.9)	64.9(7.1)	67.0(6.8)
Family history of melanoma, %	6.9	7.3	7.2	7.2
Red/blonde hair, %	14.8	14.4	14.6	14.5
Painful burn/blisters reaction as a child/adolescent, %	12.8	13.8	13.1	14.5
No. of blistering sunburns	8.2(6.9)	8.5(6.8)	8.4(6.9)	8.6(6.9)
Use of sunscreen, %	23.9	23.0	23.3	23.5
Annual UV flux ($\times 10^{-4}$ RB count)	123.3(25.4)	123.6(26.0)	123.8(25.9)	122.5(25.4)
Body mass index (kg/m^2)	26.2(5.4)	27.4(5.4)	26.6(5.4)	28.2(5.4)
Physical activity level (metabolic-equivalents hrs/wk)	18.3(23.0)	16.2(21.2)	17.5(21.8)	15.5(22.8)
Current smoking, %	10.8	9.2	9.8	9.8
Menopausal status, %	97.3	97.7	97.5	97.8
Current postmenopausal hormones use, [b] %	48.5	50.1	49.8	48.4
Total energy intake (kcal/d)	1741.6(534.0)	1722.1(531.9)	1738.3(533.9)	1696.5(527.3)
Alcohol intake (g/d)	5.4(9.3)	4.7(9.0)	5.1(9.2)	4.3(8.5)
Total citrus intake (serving/d)	0.8(0.6)	0.8(0.6)	0.8(0.6)	0.8(0.6)
Statin use, %	1.8	33.6	-	-
History of high cholesterol, %	-	-	50.6	96.9
Men in HPFS (2000)				
No. of participants	10,453	10,590	16,304	4,739
Age, years [a]	64.0(8.7)	64.6(8.3)	64.0(8.6)	65.4(8.1)
Family history of melanoma, %	4.5	4.9	4.7	4.9
Red/blonde hair, %	12.9	11.9	12.6	11.5
Painful burn/blisters reaction as a child/adolescent, %	21.7	21.8	22.1	20.8
No. of blistering sunburns	12.6(12.1)	12.6(11.9)	12.8(12.1)	12.2(11.7)

Table 2

Age- and Multivariable-Adjusted Relative Risks of Skin Cancer According to History of High Cholesterol, Nurses' Health Study (NHS, 2000–2010) and Health Professionals Follow-Up Study (HPFS, 2000–2010)

	No. of Cases	Person-Years	Age-Adjusted RR	95% CI	Multivariable-Adjusted RR*	95% CI
Basal cell carcinoma						
NHS						
No history of high cholesterol	2,215	159,784	1.00	Reference	1.00	Reference
History of high cholesterol	5,072	318,951	1.02	0.97, 1.07	1.03	0.98, 1.08
HPFS						
No history of high cholesterol	1,212	73,058	1.00	Reference	1.00	Reference
History of high cholesterol	1,702	93,196	1.06	0.99, 1.14	1.08	1.00, 1.16
Pooled†						
No history of high cholesterol	3,427	232,842	1.00	Reference	1.00	Reference
History of high cholesterol	6,774	412,147	1.03	0.99, 1.08	1.04	1.00, 1.09
Squamous cell carcinoma						
NHS						
No history of high cholesterol	298	160,676	1.00	Reference	1.00	Reference
History of high cholesterol	586	321,044	0.90	0.78, 1.04	0.94	0.82, 1.08
HPFS						
No history of high cholesterol	222	74,096	1.00	Reference	1.00	Reference
History of high cholesterol	287	94,658	0.95	0.80, 1.13	0.97	0.81, 1.16
Pooled†						
No history of high cholesterol	520	234,772	1.00	Reference	1.00	Reference
History of high cholesterol	873	415,702	0.92	0.82, 1.03	0.95	0.85, 1.06
Melanoma						
NHS						
No history of high cholesterol	87	160,872	1.00	Reference	1.00	Reference
History of high cholesterol	141	321,436	0.78	0.60, 1.03	0.77	0.58, 1.01
HPFS						
No history of high cholesterol	44	74,255	1.00	Reference	1.00	Reference

	No. of Cases	Person-Years	Age-Adjusted RR	95% CI	Multivariable-Adjusted RR*	95% CI
History of high cholesterol	61	94,839	1.07	0.73, 1.59	1.06	0.71, 1.57
Pooled†						
No history of high cholesterol	131	235,127	1.00	Reference	1.00	Reference
History of high cholesterol	202	416, 275	0.89	0.66, 1.20	0.87	0.64, 1.19

*Adjusted for family history of melanoma (yes vs. no), natural hair color (red, blonde, light brown, dark brown, black), number of arm moles (0, 1–2, 3–9, ≥10), sunburn susceptibility as a child/adolescent (none/some redness, burn, painful burn/blisters), number of lifetime blistering sunburns (0, 1–4, 5–9, ≥10), cumulative UV flux since baseline (quintiles), body mass index (<25.0, 25.0–29.9, 30.0–34.9, ≥35.0 kg/m^2), physical activity (quintiles), smoking status (never, past, or current), total energy intake (quintiles), alcohol (0, 0.1–4.9, 5.0–9.9, 10.0–19.9, ≥20.0 g/d), and citrus intake (quintiles). Analyses for women were also adjusted for menopausal status and postmenopausal hormone use.

†The multivariate-adjusted hazard ratios from each cohort were combined with meta-analytic methods using random effects model.

Table 3

Age- and Multivariable-Adjusted Relative Risks of Skin Cancer Among Women and Men with a History of High Cholesterol, According to Statin use, Nurses' Health Study (NHS, 2000–2010) and Health Professionals Follow-Up Study (HPFS, 2000–2010)

	No. of Cases	Person-Years	Age-Adjusted RR	95% CI	Multivariable-Adjusted RR*	95% CI
Basal cell carcinoma						
NHS						
No statin use	2,646	176,403	1.00	Reference	1.00	Reference
Statin use	2,426	142,548	1.01	0.95, 1.07	1.03	0.97, 1.09
HPFS						
No statin use	742	43,444	1.00	Reference	1.00	Reference
Statin use	960	49,752	1.07	0.97, 1.18	1.07	0.97, 1.18
Pooled†						
No statin use	3,388	219,847	1.00	Reference	1.00	Reference
Statin use	3,386	192,300	1.03	0.97, 1.08	1.04	0.99, 1.09
Squamous cell carcinoma						
NHS						
No statin use	319	177,555	1.00	Reference	1.00	Reference
Statin use	267	143,489	0.99	0.84, 1.17	1.03	0.87, 1.22
HPFS						
No statin use	117	44,097	1.00	Reference	1.00	Reference
Statin use	170	50,561	1.15	0.91, 1.46	1.18	0.93, 1.50
Pooled†						
No statin use	436	221,652	1.00	Reference	1.00	Reference
Statin use	437	194,050	1.04	0.90, 1.20	1.08	0.94, 1.24
Melanoma						
NHS						
No statin use	73	177,778	1.00	Reference	1.00	Reference
Statin use	68	143,657	1.11	0.79, 1.55	1.11	0.79, 1.56
HPFS						
No statin use	30	44,173	1.00	Reference	1.00	Reference

	No. of Cases	Person-Years	Age-Adjusted RR	95% CI	Multivariable-Adjusted RR*	95% CI
Statin use	31	50,666	0.94	0.56, 1.58	0.89	0.52, 1.50
Pooled†						
No statin use	103	221,951	1.00	Reference	1.00	Reference
Statin use	99	194,323	1.06	0.80, 1.40	1.04	0.78, 1.38

*Adjusted for family history of melanoma (yes vs. no), natural hair color (red, blonde, light brown, dark brown, black), number of arm moles (0, 1–2, 3–9, ≥10), sunburn susceptibility as a child/adolescent (none/some redness, burn, painful burn/blisters), number of lifetime blistering sunburns (0, 1–4, 5–9, ≥10), cumulative UV flux since baseline (quintiles), body mass index (<25.0, 25.0–29.9, 30.0–34.9, ≥35.0 kg/m^2), physical activity (quintiles), smoking status (never, past, or current), total energy intake (quintiles), alcohol (0, 0.1–4.9, 5.0–9.9, 10.0–19.9, ≥20.0 g/d), and citrus intake (quintiles). Analyses for women were also adjusted for menopausal status and postmenopausal hormone use.

†The multivariate-adjusted hazard ratios from each cohort were combined with meta-analytic methods using random effects model.

Table 4

Age- and Multivariable-Adjusted Relative Risks of Skin Cancer Among Women and Men with a History of High Cholesterol, According to Duration of Statin use, Nurses' Health Study (NHS, 2000–2010) and Health Professionals Follow-Up Study (HPFS, 2000–2010)

	No. of Cases	Person-Years	Age-Adjusted RR	95% CI	Multivariable-Adjusted RR*	95% CI
Basal cell carcinoma						
NHS						
<1 year statin use	2,322	158,556	1.00	Reference	1.00	Reference
1–2 years statin use	788	50,908	1.02	0.94, 1.11	1.05	0.96, 1.14
3–4 years statin use	658	41,587	0.99	0.91, 1.08	1.01	0.93, 1.11
5–6 years statin use	491	26,515	1.04	0.94, 1.15	1.07	0.96, 1.18
7–8 years statin use	393	20,693	1.02	0.92, 1.14	1.05	0.94, 1.17
>8 years statin use	420	20,692	0.93	0.83, 1.03	0.95	0.85, 1.06
					P-trend = 0.86	
HPFS						
<1 year statin use	660	39,363	1.00	Reference	1.00	Reference
1–2 years statin use	235	13,890	0.98	0.84, 1.14	0.98	0.85, 1.14
3–4 years statin use	265	14,140	1.06	0.92, 1.23	1.07	0.93, 1.24
5–6 years statin use	191	9,473	1.12	0.95, 1.32	1.12	0.95, 1.32
7–8 years statin use	138	7,067	1.07	0.89, 1.30	1.07	0.89, 1.30
>8 years statin use	213	9,263	1.28	1.08, 1.50	1.28	1.08, 1.50
					P-trend = 0.003	
Pooled†						
<1 year statin use	2,982	197,918	1.00	Reference	1.00	Reference
1–2 years statin use	1,023	64,798	1.02	0.95, 1.10	1.03	0.96, 1.11
3–4 years statin use	923	55,727	1.04	0.96, 1.12	1.05	0.97, 1.13
5–6 years statin use	682	35,989	1.09	1.00, 1.18	1.09	1.00, 1.19
7–8 years statin use	531	27,761	1.05	0.96, 1.15	1.05	0.95, 1.15
>8 years statin use	633	29,955	1.04	0.95, 1.14	1.03	0.94, 1.13
					P-trend = 0.20	
Squamous cell carcinoma						
NHS						

	No. of Cases	Person-Years	Age-Adjusted RR	95% CI	Multivariable-Adjusted RR*	95% CI
<1 year statin use	294	159,586	1.00	Reference	1.00	Reference
1–2 years statin use	77	51,278	0.80	0.62, 1.02	0.85	0.66, 1.09
3–4 years statin use	85	41,849	1.04	0.82, 1.33	1.10	0.86, 1.40
5–6 years statin use	55	26,686	1.04	0.77, 1.40	1.09	0.81, 1.47
7–8 years statin use	40	20,828	0.94	0.67, 1.32	0.96	0.69, 1.35
>8 years statin use	35	20,817	0.84	0.59, 1.21	0.86	0.60, 1.24
					P-trend = 0.89	
HPFS						
<1 year statin use	102	39,943	1.00	Reference	1.00	Reference
1–2 years statin use	39	14,082	1.02	0.71, 1.48	1.04	0.72, 1.51
3–4 years statin use	40	14,374	1.02	0.71, 1.48	1.07	0.74, 1.55
5–6 years statin use	50	9,636	1.83	1.28, 2.61	1.89	1.32, 2.70
7–8 years statin use	20	7,187	0.91	0.56, 1.50	0.95	0.58, 1.56
>8 years statin use	36	9,435	1.28	0.86, 1.92	1.31	0.87, 1.96
					P-trend = 0.09	
Pooled†						
<1 year statin use	396	199,529	1.00	Reference	1.00	Reference
1–2 years statin use	116	65,360	0.87	0.71, 1.07	0.90	0.73, 1.11
3–4 years statin use	125	56,224	1.07	0.87, 1.30	1.08	0.88, 1.32
5–6 years statin use	105	36,322	1.36	1.09, 1.70	1.35	1.08, 1.68
7–8 years statin use	60	28,015	1.00	0.76, 1.31	0.97	0.73, 1.28
>8 years statin use	71	30,252	1.10	0.84, 1.43	1.04	0.79, 1.35
					P-trend = 0.28	
Melanoma						
NHS						
<1 year statin use	68	159,792	1.00	Reference	1.00	Reference
1–2 years statin use	25	51,315	1.13	0.71, 1.78	1.13	0.71, 1.80
3–4 years statin use	18	41,907	0.95	0.56, 1.60	0.96	0.57, 1.62
>4 years statin use	30	68,422	0.92	0.59, 1.45	0.93	0.59, 1.47
					P-trend = 0.68	

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	No. of Cases	Person-Years	Age-Adjusted RR	95% CI	Multivariable-Adjusted RR*	95% CI
HPFS						
<1 year statin use	26	40, 008	1.00	Reference	1.00	Reference
1–2 years statin use	11	14,109	1.24	0.61, 2.53	1.22	0.60, 2.49
3–4 years statin use	6	14,397	0.67	0.27, 1.64	0.67	0.27, 1.66
>4 years statin use	18	26,326	1.11	0.58, 2.12	1.02	0.52, 1.97
					P-trend = 0.80	
Pooled†						
<1 year statin use	94	199,800	1.00	Reference	1.00	Reference
1–2 years statin use	36	65,424	1.18	0.80, 1.73	1.18	0.80, 1.74
3–4 years statin use	24	56,304	0.89	0.56, 1.40	0.89	0.56, 1.39
>4 years statin use	48	94,747	1.00	0.70, 1.44	0.97	0.67, 1.41
					P-trend = 0.68	

*Adjusted for family history of melanoma (yes vs. no), natural hair color (red, blonde, light brown, dark brown, black), number of arm moles (0, 1–2, 3–9, ≥10), sunburn susceptibility as a child/adolescent (none/some redness, burn, painful burn/blisters), number of lifetime blistering sunburns (0, 1–4, 5–9, ≥10), cumulative UV flux since baseline (quintiles), body mass index (<25.0, 25.0–29.9, 30.0–34.9, ≥35.0 kg/m^2), physical activity (quintiles), smoking status (never, past, or current), total energy intake (quintiles), alcohol (0, 0.1–4.9, 5.0–9.9, 10.0–19.9, ≥20.0 g/d), and citrus intake (quintiles). Analyses for women were also adjusted for menopausal status and postmenopausal hormone use.

†The multivariate-adjusted hazard ratios from each cohort were combined with meta-analytic methods using random effects model

Table 5

Age- and Multivariable-Adjusted Relative Risks of Skin Cancer Among Women and Men with a History of High Cholesterol, According to Type of Statin use, Nurses' Health Study (NHS, 2004–2010) and Health Professionals Follow-Up Study (HPFS, 2004–2010)

	No. of Cases	Person-Years	Age-Adjusted RR	95% CI	Multivariable-Adjusted RR*	95% CI
Basal cell carcinoma						
NHS						
No statin use	1583	87,512	1.00	Reference	1.00	Reference
Lovastatin use	117	5,797	1.06	0.88, 1.28	1.04	0.86, 1.26
Simvastatin use	394	17,803	1.02	0.91, 1.14	1.03	0.92, 1.16
Rosuvastatin use	198	10,288	1.07	0.92, 1.24	1.08	0.93, 1.25
Pravastatin use	337	22,202	0.92	0.82, 1.04	0.94	0.83, 1.06
Atorvastatin use	576	28,877	1.02	0.92, 1.12	1.03	0.94, 1.14
HPFS						
No statin use	360	19,484	1.00	Reference	1.00	Reference
Lovastatin use	29	1,406	1.06	0.72, 1.55	1.01	0.69, 1.47
Simvastatin use	197	8,637	1.15	0.97, 1.37	1.15	0.96, 1.37
Rosuvastatin use	19	1,439	0.75	0.47, 1.20	0.75	0.47, 1.20
Pravastatin use	25	2,124	0.62	0.41, 0.93	0.62	0.41, 0.93
Atorvastatin use	291	14,261	1.11	0.95, 1.30	1.11	0.95, 1.30
Pooled†						
No statin use	1,943	106,996	1.00	Reference	1.00	Reference
Lovastatin use	146	7,203	1.06	0.89, 1.25	1.03	0.87, 1.22
Simvastatin use	591	26,440	1.10	1.00, 1.20	1.09	1.00, 1.20
Rosuvastatin use	217	11,727	1.00	0.87, 1.15	1.01	0.88, 1.16
Pravastatin use	362	24,325	0.86	0.77, 0.96	0.88	0.79, 0.99
Atorvastatin use	867	43,138	1.07	0.99, 1.16	1.07	0.99, 1.16
Squamous cell carcinoma						
NHS						
No statin use	162	88,126	1.00	Reference	1.00	Reference
Lovastatin use	21	5,825	1.87	1.18, 2.95	1.82	1.15, 2.88
Simvastatin use	27	17,919	0.88	0.58, 1.33	0.91	0.60, 1.37

	No. of Cases	Person-Years	Age-Adjusted RR	95% CI	Multivariable-Adjusted RR*	95% CI
Rosuvastatin use	23	10,362	1.13	0.73, 1.77	1.17	0.75, 1.83
Pravastatin use	45	22,343	0.99	0.70, 1.40	1.03	0.73, 1.45
Atorvastatin use	44	29,080	0.86	0.61, 1.21	0.89	0.63, 1.26
HPFS						
No statin use	56	19,795	1.00	Reference	1.00	Reference
Lovastatin use	7	1,432	1.52	0.68, 3.39	1.55	0.70, 3.44
Simvastatin use	27	8,789	1.01	0.63, 1.60	1.02	0.64, 1.62
Rosuvastatin use	4	1,452	0.86	0.31, 2.39	0.91	0.33, 2.52
Pravastatin use	11	2,141	1.85	0.97, 3.53	1.78	0.92, 3.42
Atorvastatin use	52	14,512	1.29	0.88, 1.89	1.31	0.89, 1.92
Pooled†						
No statin use	218	107,920	1.00	Reference	1.00	Reference
Lovastatin use	28	7,257	1.83	1.23, 2.71	1.77	1.20, 2.63
Simvastatin use	54	26,708	0.95	0.75, 1.37	0.94	0.69, 1.27
Rosuvastatin use	27	11,814	1.05	0.71, 1.60	1.15	0.77, 1.73
Pravastatin use	56	24,484	1.07	0.78, 1.42	1.16	0.85, 1.56
Atorvastatin use	96	43,592	1.11	0.88, 1.43	1.04	0.81, 1.33
Melanoma						
NHS						
No statin use	40	88,241	1.00	Reference	1.00	Reference
Lovastatin use	3	5,839	1.11	0.34, 3.61	1.10	0.34, 3.59
Simvastatin use	6	17,939	0.70	0.29, 1.68	0.73	0.30, 1.74
Rosuvastatin use	7	10,376	1.41	0.62, 3.20	1.46	0.64, 3.33
Pravastatin use	15	22,364	1.41	0.76, 2.62	1.39	0.74, 2.60
Atorvastatin use	12	29,105	0.96	0.50, 1.87	0.96	0.49, 1.88
HPFS						
No statin use	13	19,835	1.00	Reference	1.00	Reference
Lovastatin use	2	1,437	2.01	0.44, 9.15	1.88	0.38, 9.37
Simvastatin use	6	8,805	1.05	0.40, 2.80	1.05	0.38, 2.89
Rosuvastatin use	0	1,458	0.00	0.00, 0.00	0.00	0.00, 0.00

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	No. of Cases	Person-Years	Age-Adjusted RR	95% CI	Multivariable-Adjusted RR*	95% CI
Pravastatin use	2	2,145	1.50	0.33, 6.73	1.53	0.32, 7.24
Atorvastatin use	7	14,545	0.88	0.35, 2.22	0.76	0.29, 1.99
Pooled†						
No statin use	53	108,077	1.00	Reference	1.00	Reference
Lovastatin use	5	7,276	1.32	0.53, 3.32	1.30	0.51, 3.30
Simvastatin use	12	26,744	0.87	0.46, 1.64	0.87	0.46, 1.64
Rosuvastatin use	7	11,834	1.20	0.54, 2.66	1.22	0.54, 2.71
Pravastatin use	17	24,510	1.37	0.78, 2.41	1.39	0.79, 2.45
Atorvastatin use	19	43,650	0.93	0.55, 1.58	0.90	0.52, 1.54

*Adjusted for family history of melanoma (yes vs. no), natural hair color (red, blonde, light brown, dark brown, black), number of arm moles (0, 1–2, 3–9, ≥10), sunburn susceptibility as a child/adolescent (none/some redness, burn, painful burn/blisters), number of lifetime blistering sunburns (0, 1–4, 5–9, ≥10), cumulative UV flux since baseline (quintiles), body mass index (<25.0, 25.0–29.9, 30.0–34.9, ≥35.0 kg/m^2), physical activity (quintiles), smoking status (never, past, or current), total energy intake (quintiles), alcohol (0, 0.1–4.9, 5.0–9.9, 10.0–19.9, ≥20.0 g/d), and citrus intake (quintiles). Analyses for women were also adjusted for menopausal status and postmenopausal hormone use.

†The multivariate-adjusted hazard ratios from each cohort were combined with meta-analytic methods using random effects model.