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Title: Statin Use and Skin Cancer Risk: A Prospective Cohort Study

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Abbreviations used: BCC: basal-cell carcinoma; BMI: body mass index; CI: confidence interval; E3N: *Etude Epidémiologique auprès de femmes de l'Education Nationale*; HR: hazard ratio; SCC: squamous-cell carcinoma; UVR: ultraviolet radiation.

ABSTRACT

Epidemiological studies on statin use in relation to skin cancer risk are scarce and yielded conflicting results. We explored this association in E3N, a prospective cohort of French women born in 1925-1950. Health and lifestyle data were self-reported biennially and matched with drug reimbursement data allowing to identify participants' statin use since 2004. Multivariable cause-specific hazards regression models adjusted for skin cancer risk factors estimated hazard ratios (HRs) with 95% confidence intervals (CIs). Over 2004-2014, 455 cutaneous melanoma, 1741 basal-cell carcinoma (BCC), and 268 squamous-cell carcinoma (SCC) cases were ascertained among 62,473 women. Compared with never use, there were no associations between ever use of statins and melanoma (HR=1.16, 95%CI=0.94-1.44) or SCC (HR=0.89, 95%CI=0.66-1.19) risks, and a decrease in BCC risk with ever use of statins (HR=0.89, 95%CI=0.79-0.996). We found no trend of increasing or decreasing risks with dose, duration of use, time since first use, or age at first use, and no statistically significant effect modification by pigmentary traits or residential UVR exposure. Due to the limited number of studies evaluating the associations between the use of statins and the risks of melanoma, BCC, and SCC, these findings would deserve further investigation in other settings.

INTRODUCTION

Cutaneous melanoma, basal-cell carcinoma (BCC), and squamous-cell carcinoma (SCC) are the main types of skin cancer. In 2018, ~300,000 melanomas were diagnosed worldwide, and over 60,000 people died from this cancer (Ferlay et al, 2019). According to the World Health Organization, 2-3 million BCCs and SCCs, also known as ‘keratinocyte cancers’, occur globally each year (WHO, 2017). Although their lethality is low, they require treatment, with a considerable impact on quality of life (Gaulin et al, 2015). Established risk factors for skin cancers include age, exposure to ultraviolet radiation (UVR), some pigmentary traits, sunburn history, immunosuppression and family history of skin cancer (Didona et al, 2018; Gandini et al, 2005a, 2005b).

Hydroxymethylglutaryl-coenzyme A reductase inhibitors, also known as statins, are among the most used pharmaceuticals worldwide (Weintraub, 2017). They lower blood cholesterol levels and are used for cardiovascular disease primary and secondary prevention. Beyond their action on cholesterol levels, statins have pleiotropic effects (Davies et al, 2016). Preclinical studies have suggested that they could be considered as chemopreventive or chemotherapeutic agents against cancer, including skin cancer, due to their anti-proliferative, pro-apoptotic, anti-metastatic, and anti-inflammatory properties (Kubatka et al, 2014). On the other hand, the photosensitizing (Alrashidi et al, 2020; Marguery et al, 2006; Monteiro et al, 2016; Nardi et al, 2011) and immune-modulating (Goldstein et al, 2009) effects of statins could also increase skin cancer risk.

A limited number of observational studies have evaluated the relationship between statin use and skin cancer risk. For keratinocyte cancers, they showed either positive or no association (Lin et al, 2018; Yang et al, 2017). Regarding melanoma, one observational study reported an

inverse association (Jacobs et al, 2011), while others showed no statistically significant association (Li et al, 2014; Lin et al, 2018). Of note, most studies were not able to simultaneously update statin exposure during follow-up and adjust for established skin cancer risk factors, some did not analyze BCC and SCC separately, and others used the notion of cholesterol-lowering drug use as surrogates for statin exposure. This, together with differences in populations assessed (e.g. related to UVR exposure or pigmentary traits), may explain the inconsistent results obtained so far. Inconsistencies may also illustrate the complexity of the mechanisms underlying the potential relations between statin use and skin cancer risk.

This study aims to investigate associations between statin use and skin cancer risk, considering separately melanoma, BCC and SCC, in a large prospective cohort of women, with almost 10 years of follow-up, detailed information on statin exposure from a drug reimbursement database, and available data on residential UVR and pigmentary traits. We also sought to explore whether the photosensitizing effect of statins had an impact on skin cancer risk.

RESULTS

During 583,944 woman-years of follow-up, 2,652 skin cancer cases were ascertained among 62,473 women, including 455 melanomas, 1,741 BCCs, 268 SCCs, and 188 cases of unknown type. The median follow-up time was 10.9 years (range: 0.1 to 10.9), starting at a mean age of 62.1(\pm 6.3) years.

During follow-up, 19,734 women (31.6%) had ever been exposed to statins and nearly one third (31.8%) sequentially used more than one statin type. The remaining women used exclusively atorvastatin (20.3%), pravastatin (17.0%), simvastatin (15.1%), rosuvastatin (12.4%), or

fluvastatin (3.4%). Most users were still using statins in the year preceding the end of follow-up (71.4%).

Pigmentary traits and residential UVR exposure level were similar between statin ever and never users (**Table 1**). Ever users were older and more likely to have a body mass index (BMI) ≥ 25 kg/m², a history of hypercholesterolemia, hypertension, cardiovascular disease, or diabetes, and to have ever used drugs for these conditions (**Table S1**). They also tended to have more frequent medical consultations/visits and a lower education level.

The age-adjusted hazard ratios (HRs) for melanoma, BCC, and SCC risks associated with ever vs. never use of statins were 1.17 (95% confidence interval (CI)=0.95-1.45), 0.88 (95%CI=0.79-0.99), and 0.88 (95%CI=0.66-1.19), respectively. In multivariable-adjusted models, ever use of statins was not associated with melanoma (HR=1.16, 95%CI=0.94-1.44) or SCC (HR=0.89, 95%CI=0.66-1.19) risks (**Table 2**). It was associated with a decreased BCC risk (HR=0.89, 95%CI=0.79-0.996), with statistically significant heterogeneity compared with melanoma risk ($P_{\text{homogeneity}}=0.02$). The results did not differ after further adjustment for education, BMI, smoking, comorbidities, number of medical visits, or use of other drugs (data not shown).

Among ever exposed women, we found no trend of increasing or decreasing risks with cumulative number of defined daily doses (DDD)/duration of use, average daily dose, time since first use, or age at first use (**Table 2**). We found no statistically significant heterogeneity in the HRs associated with different statin types or lipophilicity.

No significant effect modification was found by pigimentary traits, UVR exposure or family history of skin cancer (**Table 3**). Of note, however, ever use of statins was associated with an increased melanoma risk among women exposed to residential UVR doses above the median in our population (≥ 2.5 kJ/m²) at cohort inclusion (HR=1.48, 95%CI=1.09-2.00), but not among those exposed to lower UVR doses (HR=0.95, 95%CI=0.70-1.28), with a corresponding test for interaction that was close to statistical significance (P=0.052).

To better understand the increased melanoma risk associated with statin use among women exposed to residential UVR doses ≥ 2.5 kJ/m², we further stratified our analyses by residential UVR exposure at cohort inclusion cross-classified by pigimentary traits (**Table S2**). Ever use of statins was associated with an increased melanoma risk among women exposed to residential UVR doses ≥ 2.5 kJ/m² who had very fair/fair skin complexion, light brown/dark brown/black hair color, none/a few nevi, or a low skin sensitivity to the sun. However, P-values for homogeneity between categories of pigimentary traits were not statistically significant. Among women exposed to residential UVR doses ≥ 2.5 kJ/m², ever use of statins was also associated with an increased melanoma risk if taken at an average daily dose ≥ 1 DDD but not at a lower daily dose ($P_{\text{homogeneity}}=0.04$), and this association was restricted to this higher category of residential UVR exposure ($P_{\text{homogeneity}}=0.01$).

Associations did not vary significantly across anatomic sites or histologic subtypes of melanoma (**Tables S3, S4**). For SCC, the number of cases was too small to allow meaningful analyses.

The results were only slightly affected when a lag-time of 2 years (instead of one year) was applied (**Table S5**). Results of the analyses using a “new-user” design are shown in **Table S6**.

Compared with our main analysis, this analysis yielded only marginally modified HRs associated with statin ever use and categories of low numbers of cumulative DDDs, short durations of use or of time since first use. However, this approach led to a substantial loss of statistical power in categories corresponding to higher numbers of DDDs, longer durations or time since first use.

DISCUSSION

In this large cohort of women, statin ever use was associated with lower BCC risk. Conversely, it was not associated with melanoma risk overall, nor with SCC risk. We found no trend of increasing or decreasing risks with cumulative dose, duration of use, time since first use, or age at first use, and no statistically significant effect modification by pigmentary traits or residential UVR exposure.

Our findings of an inverse association between statin ever use and BCC risk contrasts with previous reports. The most recent meta-analysis reporting on the relationship between statin use and keratinocyte cancer risk found no significant association based on data from 14 randomized controlled trials (relative risk=1.09, 95%CI=0.85-1.39) but increased risk based on data from four observational studies (relative risk= 1.11, 95%CI= 1.02-1.22) (Yang et al, 2017). However, some of these studies included both women and men while we included women only. Other sources of discrepancy may include the fact that some previous studies combined results for both keratinocyte cancers (Haukka et al, 2010; Li et al, 2014; Wang et al, 2016), or lacked consideration of sunlight exposure or pigmentary traits. The only observational study not included in the above-mentioned meta-analysis reported no association in women from the Nurses' Health Study between self-reported statin use and BCC risk, although the analysis was adjusted for cumulative UV flux since baseline and pigmentary traits (Lin et al, 2018).

However, our findings of an inverse association between statin use and BCC risk is consistent with some laboratory studies which suggested that statins could protect against keratinocyte cancers by lowering cellular cholesterol levels - which leads to apoptosis of keratinocytes (Gniadecki, 2004) - and could prevent BCC by inhibiting Smoothened (Smo) signalling in the hedgehog signalling pathway - which transmits information to embryonic cells for proper cell differentiation and has been shown to play a critical role in the development of BCC in particular (Tang et al, 2007).

Regarding melanoma, our result of an overall null association with statin use is consistent with the latest meta-analysis reporting no association (relative risk=0.94, 95% CI=0.85-1.04) based on data from 17 randomized-controlled trials, 5 case-control studies, and 2 cohort studies (Li et al, 2014). The only observational study published thereafter on the statin-melanoma risk relationship also showed no significant association in women from the Nurses' Health Study (HR=1.11, 95%CI=0.79-1.56) (Lin et al, 2018).

However, we reported that ever use of statins was associated with an increased melanoma risk among women exposed to higher residential UVR doses, although effect modification by that factor did not reach statistical significance ($P=0.052$). An effect modification by UVR residential doses would be consistent with an influence of the photosensitizing effect of statins on skin cancer risk. The photosensitizing effect of other drugs was indeed shown to be a possible cause of skin lesions and melanoma (Miller et al, 2010; O'Gorman & Murphy, 2014; Siiskonen et al, 2013). Among women exposed to higher residential UVR doses, our finding of a higher statin-associated melanoma risk in those less at risk (dark hair color, few nevi, or low skin sensitivity to the sun) might be explained by riskier sun exposure behaviours. In addition, a higher melanoma risk among those with an average daily dose of statins ≥ 1 DDD could be explained by a dose-dependent reaction of phototoxicity due to statins as with other

photosensitizing agents (Ljunggren et al, 1981). However, despite the consistency of our findings, effect modification by UVR exposure did not reach statistical significance and we cannot exclude chance findings given the small number of cases in some categories. Potential effect modification by that factor should thus be investigated further in future studies.

The main strengths of our study include the use of a large prospective cohort with detailed information from a drug reimbursement database to identify statin exposure, which minimized risk of recall bias and provided precise information on statin use. In France, statins are prescription-only medications that are all eligible for reimbursement by the health insurance system. We can thus expect that we could identify almost all purchased statin boxes, although we recognize that some women may not have consumed all the medications they purchased. To our knowledge, no previous study evaluated a potential effect modification of the statin-skin cancers risks associations by sun exposure and pigimentary traits, which sheds light on the potential impact of the photosensitizing effect of statins. Another strength of our study is that E3N cohort is formed with members of a health insurance plan that primarily covered teachers. They are, on average, highly educated and motivated women ensuring high reliability of the answers given to the questionnaires, with validation studies revealing very satisfactory results, and a high follow-up questionnaire response rate (Clavel-Chapelon, 2015). We were able to adjust for some important skin cancer risk factors and consider information on a variety of other potential confounders available from the reimbursement database and biennial questionnaires. Because statin users may have increased opportunity for skin cancer diagnosis due to more frequent medical visits, we verified that adjustment for the number of previous medical consultations did not impact our results. However, we cannot exclude potential residual confounding. Moreover, the lack of data on recreational UVR exposure and sun protection behaviors limited our ability to fully explore the potential influence of the photosensitizing

effect of statins on skin cancer risk. Another limitation was the small number of cases in some categories (especially for SCC) and the multiplicity of statistical tests that could lead to isolated false positive results. Furthermore, we included prevalent users in our analyses, which would tend to under-ascertain events occurring shortly after statin initiation (Ray, 2003) and prevented us to know the exact dose/duration/time since first use/age at first use for those women who had started statin use before January 1, 2004. The “new-user design” approach that we implemented as a supplementary analysis, while reducing misclassification of drug use due to left truncation of the time period used for exposure ascertainment in prevalent users, unfortunately led to an important loss of statistical power, especially for estimating HRs of skin cancer associated with relatively long durations of use or long periods following treatment initiation, which is an important drawback when studying an outcome such as cancer and may hinder a meaningful evaluation. Finally, our analyses involved women over 50 and therefore cannot be extrapolated to men and younger women.

In conclusion, in this large prospective cohort of women, we found no association overall between statin use and melanoma or SCC risks. Statin use was associated with a decreased BCC risk. There were some suggestions of an increased melanoma risk associated with the use of statins among women with higher residential UVR exposure which should be investigated further in future studies.

MATERIALS AND METHODS

The E3N cohort

E3N (*Etude Epidémiologique auprès de femmes de l'Education Nationale*) is an ongoing prospective cohort study involving 98,995 French women born in 1925-1950 and insured by a national health scheme covering workers from the French national education system and their

families (Clavel-Chapelon, 2015). Women were enrolled in 1990 after returning a self-administered questionnaire on their lifestyle and medical history along with a written informed consent. Thereafter follow-up questionnaires were sent every 2-3 years, with a response rate >75% at each follow-up. For each participant, the health scheme provided data that included all outpatient reimbursements for health expenditures since January 1, 2004. The E3N cohort was conducted in accordance with the Declaration of Helsinki and received ethical approval from the French National Commission for Data Protection and Privacy. It was registered at clinicaltrials.gov as NCT03285230 on September 15, 2017.

Identification of cases

Skin cancer events were self-reported in the questionnaires or identified from the national cause-of-death registry. Pathology reports were requested from women or their doctors, allowing the extraction of data on tumor characteristics. Overall, 75% of melanomas, 74% of BCCs, and 81% of SCCs were documented with complementary medical information. Among self-reported skin cancers for which we could obtain medical information (from pathology reports, other medical document or through contact with participants' physicians) only 5.8% were not confirmed by the information obtained. Self-reported events for which no complementary information could be obtained were thus included as cases in the current analysis.

Data collection

Exposure to statins

Exposure to statins was assessed through the health expenditure reimbursement database, which contains, for each reimbursed drug delivery, date of purchase, molecule, number of tablets per package, and dose per tablet. Statins were identified by their Anatomical Therapeutic Chemical

code [C10AA (statins), C10BA (statins in combination with other lipid-modifying agents), and C10BX (statins in combination with other drugs)], and the corresponding DDD, the assumed average daily maintenance dose for a type used for its main indication in adults, was available from the World Health Organisation Collaborating Centre for Drug Statistics Methodology (WHO, 2019).

“Ever use” of statins was defined as at least two reimbursements of the drug of interest during any previous 3-month period or at least one reimbursement for a 3-month box (i.e., containing at least 70 tablets) since January 1, 2004. It was further classified according to cumulative number of DDDs, cumulative duration of use, average daily dose, time since first use, age at first use, type, and lipophilicity (see footnotes to Table 2).

Women with a statin reimbursement between January 1, 2004 and April 1, 2004 were likely to have begun use before the availability of reimbursement data. Since in this case exposure data is likely subject to left truncation, women with statin reimbursements over this period were assigned to an “unknown” dose/duration/time since first use/age at first use category, unless they could be assigned to a “ $\geq x$ ” duration/dose/time since first use or a “ $< x$ ” age at first use category.

Skin cancer risk factors

Residential UVR exposure at birth and at inclusion was estimated by linkage to a European database containing mean daily UVR doses in French counties (Verdebout, 2004). Pigmentary characteristics were self-reported at inclusion and included hair color, skin complexion, number of nevi, number of freckles, and skin sensitivity to sun exposure (see Table 1 for characteristic categories). Family history of skin cancer in first-degree relatives was collected in 2000.

Other covariates

BMI was computed at each questionnaire. Education level and smoking status were reported at inclusion and smoking status was updated regularly during follow-up. Personal history of cardiovascular diseases (lower limb arteritis, myocardial infarction, angina pectoris, stroke, and hypertension), diabetes, and hypercholesterolemia were collected through all questionnaires sent before January 1st, 2004, with subsequent updates in 2005, 2008, and 2011. Ever use of other drugs (defined as at least two reimbursements of the drug during any previous 3-month period or at least one reimbursement for a 3-month box since January 1, 2004) likely to be also used by statin users [fibrates (C10AB), other lipid-lowering drugs (C10AC, C10AD, C10AX, and C10BA), non-steroidal anti-inflammatory drugs (M01A, N02BA, and N02BG04), platelet aggregation inhibitors excluding heparin (B01AC and C10BX02), blood glucose-lowering drugs excluding insulins (A10B), and anti-hypertensive drugs (C02, C03, C07, C08, and C09)], was assessed using the healthcare reimbursement database. Finally, that database allowed us to identify women's general practitioner or specialist consultations/visits.

Study population and follow-up

Follow-up started on January 1st, 2004 until the first date of diagnosis of any skin cancer or any other cancer, date of the last returned questionnaire, or November 17th, 2014, whichever occurred first. Women who were lost to follow-up from baseline (n=16,013), reported a history of cancer (including BCC) at baseline (n=11,405), were no longer covered by the health scheme (n=3808), with missing data on residential UVR exposure at birth (n=5296) were excluded, leaving a final sample of 62,473 women for analysis.

Statistical analyses

HRs and 95% CIs of the a statin-skin cancer incidence associations were estimated using Cox proportional hazards regression models with age as the time scale, stratified by birth cohort (in 5-year categories). Multivariable-adjusted models included pigimentary traits, residential UVR exposure in county of birth and of residence at inclusion, and family history of skin cancer. In separate models, we tested the influence of additional adjustment for ever use of other drugs (as listed above), lifetime history of cardiovascular diseases, diabetes, and hypercholesterolemia, which are also more frequent in statin users vs. non users, BMI (<18.5, 18.5-22.4, 22.5-24.9, 25.0-29.9, \geq 30.0 kg/m²), education (<12, 12-14, \geq 15 years), number of medical consultations/visits in the previous 6 months (0, 1-3, >3), and smoking status (never, current, former smoker).

Statin exposure was time-varying: participants classified as ever users at the end of follow-up contributed person-time as non-exposed until reaching their second reimbursement within a 3-month period, or their first reimbursement for a 3-month box. Characteristics of exposure such as cumulative number of DDDs, covariates from the health expenditure database, comorbidities, smoking status, and BMI were also time-varying.

Statin use, as well as exposure to other drugs and number of medical visits/consultations, were lagged by 1 year in order to minimize protopathic bias and impose a reasonable induction period for an effect on skin cancer incidence (Pottegård & Hallas, 2017). In a sensitivity analysis, use was lagged by 2 years in order to assess the stability of the results.

We tested for effect modification by established skin cancer risk factors by adding cross-product interaction terms in the models.

We also stratified analyses according to anatomic site, and additionally by histologic subtype for melanoma, using competing-risk models with the cause-specific hazards approach (Pintilie et al, 2007): we ran separate Cox proportional hazards regression models for each specific skin cancer site/sub-type, excluding cases with missing information on site/sub-type, and censoring at the date of their diagnosis cases with a skin cancer other than that under study. Homogeneity tests were performed using Chi-square statistics to compare estimates over strata.

Missing values in covariates were imputed to the median or to the modal category if occurring in <5% of observations, which has proven to be satisfactory in our data (Garcia-Acosta & Clavel-Chapelon, 1999); otherwise a missing category was created.

We performed a sensitivity analysis excluding women reimbursed with statins in 2004 or 2005, and with the start of follow-up set at January 1, 2006. With that “new-user design” (Ray 2003), characteristics of use such as dose/duration/time since first use/age at first use are less subject to left truncation, allowing exact values to be used in trend analyses.

All statistical tests were two-sided, and significance was set at the .05 level. Analyses were performed using SAS, version 9.4 (SAS Institute Inc.).

DATA AVAILABILITY STATEMENT

Data on E3N cohort participants are available to bona fide researchers for all type of health-related research, which is in the public interest. Data are made available under managed access owing to governance constraints and need to protect the privacy of study participants. Raw data requests should be submitted through the E3N website (www.e3n.fr) or sent to contact@e3n.fr

and will be reviewed by the E3N Access Committee. Further information is provided at <https://www.e3n.fr/node/78>.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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AUTHORS CONTRIBUTIONS

Conceptualization: MK, AF; Data Curation: MAR, AF; Formal Analysis: MAR; Funding Acquisition: MAR, MK, AF; Investigation: MAR, MK, AF; Methodology: MK, AF; Project Administration: MK, AF; Resources: GS, MCBR, MK, AF; Software: MAR, AF; Supervision: MK, AF; Visualization: MAR; Validation: MK, AF; Writing - Original Draft Preparation: MAR, RG, TER, MK, AF; Writing - Review and Editing: MAR, RG, MC, YMS, IC, GS, MCBR, TER, MK, AF.

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Table 1. Selected characteristics of study participants¹ according to statin exposure at the end of follow-up, E3N cohort (n=62,473), France, 2004-2014

| Characteristic | Never used statins n=42,739 | Ever used statins n=19,734 |
|--|--------------------------------|-------------------------------|
| Age (years) (mean, SD) | 61.6 ± 6.2 | 63.2 ± 6.4 |
| Body Mass Index (kg/m²) (mean, SD) | 23.5 ± 3.7 | 24.5 ± 3.9 |
| Skin color | | |
| Very fair | 470 (1.1) | 197 (1.0) |
| Fair | 25,259 (59.1) | 11,505 (58.3) |
| Medium | 16,454 (38.5) | 7756 (39.3) |
| Dark and very dark | 556 (1.3) | 276 (1.4) |
| Hair color | | |
| Red | 727 (1.7) | 276 (1.4) |
| Blond | 4231 (9.9) | 1993 (10.1) |
| Light brown | 25,985 (60.8) | 12,097 (61.3) |
| Dark brown | 9873 (23.1) | 4500 (22.8) |
| Black | 1923 (4.5) | 868 (4.4) |
| Number of nevi | | |
| Very many | 4487 (10.5) | 1954 (9.9) |
| Many | 18,720 (43.8) | 8505 (43.1) |
| A few | 15,557 (36.4) | 7262 (36.8) |
| None | 3975 (9.3) | 2013 (10.2) |
| Number of freckles | | |
| Very many | 2137 (5.0) | 927 (4.7) |
| Many | 12,565 (29.4) | 5644 (28.6) |
| A few | 10,514 (24.6) | 4776 (24.2) |
| None | 17,523 (41.0) | 8387 (42.5) |
| Skin sensitivity to sun exposure | | |
| High | 11,967 (28.0) | 5683 (28.8) |
| Moderate | 21,455 (50.2) | 9532 (48.3) |
| Low | 9317 (21.8) | 4519 (22.9) |
| Residential UVR exposure at birth (kJ/m²) (mean, SD) | 2.5 ± 0.2 | 2.5 ± 0.2 |
| Residential UVR exposure at inclusion (kJ/m²) (mean, SD) | 2.6 ± 0.2 | 2.5 ± 0.3 |
| Family history of skin cancer (yes) | 427 (1.0) | 197 (1.0) |
| Number of medical visits during the preceding 6 months² | | |
| 0 | 2906 (6.8) | 493 (2.5) |
| [1-3[| 12,694 (29.7) | 4815 (24.4) |
| ≥ 3 | 27,139 (63.5) | 14,426 (73.1) |

Abbreviations: UVR: ultraviolet radiation.

¹ All parameters are given at baseline and as n (%), except when mentioned otherwise.

² At the end of the follow-up.

Table 2. Associations between statin exposure and skin cancers risks, E3N cohort (n=62,473), France, 2004-2014

| | Melanoma | | BCC | | SCC | |
|--|-----------|----------------------------|-----------|----------------------------|-----------|----------------------------|
| | No. cases | HR ^{1,2} (95% CI) | No. cases | HR ^{1,2} (95% CI) | No. cases | HR ^{1,2} (95% CI) |
| Statin exposure | | | | | | |
| Never | 333 | ref | 1367 | ref | 207 | ref |
| Ever | 122 | 1.16 (0.94 - 1.44) | 374 | 0.89 (0.79 - 0.996) | 61 | 0.89 (0.66 - 1.19) |
| Cumulative number of DDDs | | | | | | |
| Never exposed | 333 | ref | 1367 | ref | 207 | ref |
| < 300 DDD | 35 | 1.38 (0.97 - 1.96) | 96 | 0.93 (0.76 - 1.15) | 17 | 1.06 (0.65 - 1.75) |
| ≥ 300 - < 900 DDD | 24 | 1.12 (0.74 - 1.70) | 76 | 0.90 (0.71 - 1.13) | 7 | 0.53 (0.25 - 1.12) |
| ≥ 900 DDD | 37 | 1.16 (0.82 - 1.65) | 101 | 0.79 (0.64 - 0.97) | 21 | 0.98 (0.62 - 1.57) |
| Unknown | 26 | 1.00 (0.67 - 1.49) | 101 | 0.94 (0.77 - 1.15) | 16 | 0.89 (0.54 - 1.49) |
| <i>P</i> _{trend} ³ | | 0.93 | | 0.38 | | 0.94 |
| Cumulative duration of exposure (years)⁴ | | | | | | |
| Never exposed | 333 | ref | 1367 | ref | 207 | ref |
| < 1 year | 29 | 1.32 (0.90 - 1.94) | 83 | 0.93 (0.75 - 1.16) | 15 | 1.07 (0.63 - 1.82) |
| ≥ 1 - < 3 years | 27 | 1.26 (0.85 - 1.88) | 78 | 0.91 (0.73 - 1.15) | 9 | 0.67 (0.34 - 1.32) |
| ≥ 3 years | 42 | 1.11 (0.79 - 1.55) | 120 | 0.79 (0.65 - 0.96) | 22 | 0.89 (0.56 - 1.41) |
| Unknown | 24 | 1.02 (0.67 - 1.54) | 93 | 0.95 (0.77 - 1.18) | 15 | 0.91 (0.54 - 1.54) |
| <i>P</i> _{trend} ³ | | 0.77 | | 0.41 | | 0.60 |
| Average daily dose (DDD)⁵ | | | | | | |
| Never exposed | 333 | ref | 1367 | ref | 207 | ref |
| < 1 DDD | 97 | 1.10 (0.88 - 1.39) | 314 | 0.89 (0.78 - 1.01) | 54 | 0.95 (0.70 - 1.29) |
| ≥ 1DDD | 25 | 1.47 (0.98 - 2.22) | 60 | 0.87 (0.67 - 1.12) | 7 | 0.61 (0.29 - 1.30) |
| <i>P</i> _{trend} ³ | | 0.24 | | 0.85 | | 0.32 |
| Time since first exposure (years) | | | | | | |
| Never exposed | 333 | ref | 1367 | ref | 207 | ref |
| < 4 years | 48 | 1.38 (1.02 - 1.87) | 135 | 0.97 (0.81 - 1.15) | 18 | 0.83 (0.51 - 1.35) |
| ≥ 4 years | 54 | 1.04 (0.77 - 1.41) | 164 | 0.80 (0.67 - 0.95) | 33 | 1.01 (0.68 - 1.50) |
| Unknown | 20 | 1.08 (0.68 - 1.71) | 75 | 0.95 (0.75 - 1.21) | 10 | 0.73 (0.38 - 1.39) |
| <i>P</i> _{trend} ³ | | 0.87 | | 0.15 | | 0.62 |
| Age at first exposure (years) | | | | | | |
| Never exposed | 333 | ref | 1367 | ref | 207 | ref |
| < 60 years old | 29 | 1.18 (0.80 - 1.76) | 95 | 1.04 (0.84 - 1.29) | 10 | 0.95 (0.49 - 1.86) |
| ≥ 60 years old | 56 | 1.22 (0.90 - 1.63) | 166 | 0.88 (0.75 - 1.04) | 23 | 0.73 (0.47 - 1.13) |
| Unknown | 37 | 1.08 (0.76 - 1.53) | 113 | 0.78 (0.64 - 0.95) | 28 | 1.06 (0.70 - 1.59) |
| <i>P</i> _{trend} ³ | | 0.72 | | 0.16 | | 0.89 |
| Type (Ever exposure) | | | | | | |
| Never exposed | 333 | ref | 1367 | ref | 207 | ref |
| Atorvastatin | 40 | 1.03 (0.74 - 1.43) | 120 | 0.83 (0.69 - 1.00) | 25 | 1.11 (0.73 - 1.68) |
| Simvastatin | 39 | 1.33 (0.95 - 1.85) | 102 | 0.92 (0.75 - 1.13) | 13 | 0.69 (0.39 - 1.21) |
| Pravastatin | 38 | 1.05 (0.75 - 1.47) | 128 | 0.95 (0.79 - 1.14) | 19 | 0.84 (0.52 - 1.35) |

| | | | | | | |
|----------------------------------|-----|--------------------|------|--------------------|-----|--------------------|
| Fluvastatin | 12 | 1.13 (0.64 - 2.02) | 37 | 0.99 (0.71 - 1.37) | 4 | 0.64 (0.24 - 1.73) |
| Rosuvastatin | 23 | 0.91 (0.59 - 1.41) | 78 | 0.92 (0.73 - 1.16) | 13 | 1.01 (0.57 - 1.80) |
| <i>P</i> _{homogeneity} | | 0.71 | | 0.85 | | 0.65 |
| Lipophilicity⁶ | | | | | | |
| Never exposed | 333 | ref | 1367 | ref | 207 | ref |
| Lipophilic | 67 | 1.27 (0.97 - 1.65) | 188 | 0.89 (0.76 - 1.03) | 32 | 0.92 (0.63 - 1.35) |
| Hydrophilic | 40 | 1.13 (0.81 - 1.58) | 133 | 0.92 (0.77 - 1.11) | 20 | 0.86 (0.54 - 1.37) |
| Lipophilic and hydrophilic | 15 | 0.90 (0.53 - 1.52) | 53 | 0.81 (0.61 - 1.06) | 9 | 0.85 (0.43 - 1.67) |
| <i>P</i> _{homogeneity} | | 0.51 | | 0.72 | | 0.97 |

Abbreviations: BCC: basal-cell carcinoma; CI: confidence interval; DDD: defined daily dose; HR: hazard ratio; SCC: squamous-cell carcinoma.

¹ Model with exposure lagged by one year, stratified by year of birth and adjusted for age (time scale), residential UVR exposure at birth and at inclusion, pigmentary traits, and family history of skin cancer.

² Excluding the 188 skin cancer cases of unknown type.

³ Tests for linear trend were performed among ever exposed participants, using an ordinal variable across categories, except for average daily dose for which we could use exact values.

⁴ Duration of use was calculated, for each box delivered, as the shortest length of time between the standard duration of the box and time until the next statin purchase. The standard duration of a statin box (in days) was assumed to be equal to the number of tablets it contained, assuming a consumption of one tablet per day. Cumulative duration of use was calculated as the sum of durations of use corresponding to each delivery since January 1, 2004.

⁵ The average daily dose (DDD/day) was calculated as the cumulative number of DDDs divided by cumulative duration of use.

⁶ Lipophilic statins include atorvastatin, simvastatin and fluvastatin while hydrophilic statins include rosuvastatin and pravastatin.

Table 3. Associations between ever use (vs. never use) of statins and skin cancer risks in strata of skin cancer risk factors, E3N cohort (n= 62,473), France, 2004-2014

| | Melanoma | | | BCC | | | SCC | | |
|---|------------------------|----------------------------|----------------|------------------------|----------------------------|----------------|------------------------|----------------------------|----------------|
| | No. cases ³ | HR ^{1,2} (95% CI) | P ⁴ | No. cases ³ | HR ^{1,2} (95% CI) | P ⁴ | No. cases ³ | HR ^{1,2} (95% CI) | P ⁴ |
| Skin color | | | | | | | | | |
| Very fair/fair | 89 | 1.35 (1.04 - 1.73) | 0.09 | 251 | 0.91 (0.78 - 1.04) | 0.55 | 48 | 0.99 (0.71 - 1.39) | 0.28 |
| Medium/dark/very dark | 33 | 0.86 (0.58 - 1.27) | | 123 | 0.85 (0.69 - 1.04) | | 13 | 0.64 (0.34 - 1.18) | |
| Hair color | | | | | | | | | |
| Blond | 16 | 1.22 (0.67 - 2.21) | 0.79 | 40 | 0.88 (0.61 - 1.26) | 0.38 | 10 | 0.83 (0.40 - 1.72) | 0.25 |
| Red | 4 | 1.89 (0.49 - 7.33) | | 3 | 0.38 (0.11 - 1.25) | | 3 | 1.11 (0.23 - 5.32) | |
| Light brown | 78 | 1.14 (0.88 - 1.49) | | 245 | 0.93 (0.80 - 1.07) | | 40 | 1.03 (0.71 - 1.49) | |
| Dark brown/black | 24 | 1.16 (0.72 - 1.87) | | 86 | 0.82 (0.65 - 1.05) | | 8 | 0.52 (0.24 - 1.11) | |
| Number of nevi | | | | | | | | | |
| Very many | 24 | 0.90 (0.57 - 1.43) | 0.11 | 42 | 0.75 (0.53 - 1.06) | 0.69 | 11 | 1.37 (0.64 - 2.92) | 0.37 |
| Many | 51 | 1.10 (0.80 - 1.53) | | 167 | 0.93 (0.78 - 1.11) | | 24 | 0.83 (0.52 - 1.31) | |
| A few | 37 | 1.42 (0.95 - 2.12) | | 132 | 0.87 (0.71 - 1.06) | | 22 | 0.92 (0.56 - 1.50) | |
| None | 10 | 2.20 (0.92 - 5.27) | | 33 | 0.96 (0.64 - 1.43) | | 4 | 0.51 (0.17 - 1.52) | |
| Number of freckles | | | | | | | | | |
| Very many | 10 | 0.86 (0.42 - 1.77) | 0.80 | 17 | 0.64 (0.38 - 1.08) | 0.35 | 4 | 0.76 (0.26 - 2.29) | 0.70 |
| Many | 44 | 1.11 (0.78 - 1.58) | | 125 | 0.88 (0.72 - 1.08) | | 24 | 0.81 (0.51 - 1.28) | |
| A few | 28 | 1.22 (0.78 - 1.90) | | 104 | 0.96 (0.77 - 1.21) | | 17 | 1.20 (0.68 - 2.13) | |
| None | 40 | 1.32 (0.90 - 1.94) | | 128 | 0.87 (0.72 - 1.07) | | 16 | 0.84 (0.47 - 1.50) | |
| Skin sensitivity to sun exposure | | | | | | | | | |
| High | 38 | 1.02 (0.70 - 1.49) | 0.71 | 130 | 0.95 (0.77 - 1.16) | 0.47 | 22 | 0.81 (0.50 - 1.31) | 0.69 |
| Moderate | 63 | 1.19 (0.88 - 1.60) | | 183 | 0.89 (0.75 - 1.05) | | 31 | 1.03 (0.68 - 1.56) | |
| Low | 21 | 1.53 (0.90 - 2.62) | | 61 | 0.77 (0.58 - 1.03) | | 8 | 0.70 (0.31 - 1.57) | |
| Residential UVR exposure at birth (kJ/m²) | | | | | | | | | |
| < 2.5 | 65 | 1.05 (0.79 - 1.40) | 0.47 | 182 | 0.85 (0.72 - 1.01) | 0.46 | 41 | 1.08 (0.74 - 1.56) | 0.050 |
| ≥ 2.5 | 57 | 1.32 (0.97 - 1.82) | | 192 | 0.92 (0.78 - 1.09) | | 20 | 0.66 (0.41 - 1.08) | |
| Residential UVR exposure at inclusion (kJ/m²) | | | | | | | | | |
| < 2.5 | 58 | 0.95 (0.70 - 1.28) | 0.052 | 186 | 0.87 (0.74 - 1.03) | 0.51 | 41 | 1.10 (0.76 - 1.60) | 0.08 |
| ≥ 2.5 | 64 | 1.48 (1.09 - 2.00) | | 188 | 0.90 (0.76 - 1.07) | | 20 | 0.64 (0.39 - 1.04) | |
| Family history of skin cancer | | | | | | | | | |
| No | 120 | 1.15 (0.93 - 1.42) | 0.48 | 369 | 0.89 (0.79 - 1.00) | 0.69 | 60 | 0.91 (0.68 - 1.22) | 0.53 |
| Yes | 2 | 5.31 (0.57 - 49.39) | | 5 | 0.73 (0.27 - 1.96) | | 1 | 0.26 (0.02 - 2.87) | |

Abbreviations: BCC: basal-cell carcinoma; CI: confidence interval; HR: hazard ratio; SCC: squamous-cell carcinoma; UVR: ultraviolet radiation.

¹ Model with exposure lagged by one year, stratified by year of birth and adjusted for age (time scale), residential UVR exposure at birth and at inclusion, pigmentary traits, and family history of skin cancer.

² Excluding the 188 skin cancer cases of unknown type.

³ Number of cases ever exposed to statins.

⁴ P_{interaction}

Table S1. Other characteristics of study participants¹ according to statin exposure at the end of follow-up, E3N cohort (n=62,473), France, 2004-2014

| Characteristic | Never used statins n=42,739 | Ever used statins n=19,734 |
|---|--------------------------------|-------------------------------|
| Year of birth | | |
| < 1930 | 2265 (5.3) | 1362 (6.9) |
| 1930-1934 | 4060 (9.5) | 2743 (13.9) |
| 1935-1939 | 7308 (17.1) | 4223 (21.4) |
| 1940-1945 | 10,557 (24.7) | 4973 (25.2) |
| ≥ 1945 | 18,549 (43.4) | 6433 (32.6) |
| Education level | | |
| < 12 years | 4103 (9.6) | 2526 (12.8) |
| [12-14[years | 22,609 (52.9) | 11,229 (56.9) |
| ≥ 15 years | 16,027 (37.5) | 5979 (30.3) |
| Smoking | | |
| Never-smoker | 22,524 (52.7) | 10,696 (54.2) |
| Current smoker | 4359 (10.2) | 2072 (10.5) |
| Ex-smoker | 15,856 (37.1) | 6966 (35.3) |
| Body Mass Index (kg/m²) | | |
| <18.5 | 1538 (3.6) | 414 (2.1) |
| [18.5-22.5[| 17,908 (41.9) | 6117 (31.0) |
| [22.5-25[| 11,668 (27.3) | 5743 (29.1) |
| [25-30[| 9189 (21.5) | 5644 (28.6) |
| ≥30 | 2436 (5.7) | 1816 (9.2) |
| Residential UVR exposure at birth (kJ/m²) (quartiles) | | |
| < 2.4 | 9574 (22.4) | 4795 (24.3) |
| [2.4-2.5[| 11 411 (26.7) | 5210 (26.4) |
| [2.5-2.7[| 10,044 (23.5) | 4559 (23.1) |
| ≥ 2.7 | 11,710 (27.4) | 5170 (26.2) |
| Residential UVR exposure at inclusion (kJ/m²) (quartiles) | | |
| < 2.4 | 9061 (21.2) | 4697 (23.8) |
| [2.4-2.5[| 11,753 (27.5) | 5308 (26.9) |
| [2.5-2.7[| 9744 (22.8) | 4302 (21.8) |
| ≥ 2.7 | 12,181 (28.5) | 5427 (27.5) |
| Lifetime history of selected diseases ² | | |
| Lower limb arteritis (yes) | 299 (0.7) | 395 (2.0) |
| Angina pectoris (yes) | 470 (1.1) | 928 (4.7) |
| Stroke (yes) | 983 (2.3) | 1164 (5.9) |
| Myocardial infarction (yes) | 86 (0.2) | 513 (2.6) |
| Hypertension (yes) | 12,480 (29.2) | 9018 (45.7) |
| Diabetes (yes) | 1667 (3.9) | 2151 (10.9) |
| Hypercholesterolemia (yes) | 14,574 (34.1) | 15,195 (77.0) |
| Use of selected drugs during follow-up ² | | |
| Fibrates (yes) | 3761 (8.8) | 4006 (20.3) |
| Lipid lowering drugs other than statins or fibrates (yes) | 727 (1.7) | 2940 (14.9) |
| NSAIDs (yes) | 31,413 (73.5) | 15,491 (78.5) |
| Platelet aggregation inhibitors, excl.heparin (yes) | 5300 (12.4) | 6848 (34.7) |
| Blood glucose lowering drugs, excl.insulins (yes) | 1881 (4.4) | 2565 (13.0) |
| Antihypertensives (yes) | 18,592 (43.5) | 13,103 (66.4) |

Abbreviations: NSAIDs: Nonsteroidal anti-inflammatory drugs; UVR: ultraviolet radiation.

¹ All parameters are given at baseline and as n (%), except when mentioned otherwise.

² At the end of the follow-up.

Table S2. Associations between ever use (vs. never) of statins and melanoma risk in strata of residential UVR exposure cross-classified by pigimentary traits, and according to daily dose, E3N cohort (n= 62,473), France, 2004-2014

| Residential UVR exposure at inclusion (kJ/m ²) | < 2.5 | | ≥ 2.5 | | <i>P</i> _{homogeneity} ³ |
|--|------------------------|-------------------------|------------------------|---------------------------|--|
| | No. cases ¹ | HR ² (95%CI) | No. cases ¹ | HR ² (95%CI) | |
| Skin color | | | | | |
| Very fair/fair | 45 | 1.12 (0.79 - 1.58) | 44 | 1.73 (1.19 - 2.52) | 0.03 |
| Medium/dark/very dark | 13 | 0.63 (0.34 - 1.16) | 20 | 1.16 (0.68 - 1.96) | 0.98 |
| <i>P</i> _{homogeneity} ⁴ | | 0.13 | | 0.26 | |
| Hair color | | | | | |
| Blond/red | 12 | 1.32 (0.65 - 2.68) | 8 | 1.29 (0.55 - 3.01) | 0.91 |
| Light brown/dark brown/black | 46 | 0.88 (0.63 - 1.23) | 56 | 1.52 (1.10 - 2.11) | 0.04 |
| <i>P</i> _{homogeneity} ⁴ | | 0.20 | | 0.51 | |
| Number of nevi | | | | | |
| None/a few | 19 | 1.02 (0.59 - 1.74) | 28 | 2.39 (1.43 - 4.00) | 0.004 |
| Many/very many | 39 | 0.94 (0.65 - 1.35) | 36 | 1.15 (0.78 - 1.70) | 0.91 |
| <i>P</i> _{homogeneity} ⁴ | | 0.75 | | 0.07 | |
| Number of freckles | | | | | |
| None/a few | 32 | 1.09 (0.72 - 1.65) | 36 | 1.48 (0.99 - 2.22) | 0.30 |
| Many/very many | 26 | 0.81 (0.52 - 1.26) | 28 | 1.48 (0.93 - 2.35) | 0.19 |
| <i>P</i> _{homogeneity} ⁴ | | 0.25 | | 0.77 | |
| Skin sensitivity to sun exposure | | | | | |
| Low | 8 | 1.02 (0.44 - 2.36) | 13 | 2.10 (1.03 - 4.28) | 0.21 |
| Moderate | 28 | 0.96 (0.62 - 1.48) | 35 | 1.46 (0.97 - 2.20) | 0.21 |
| High | 22 | 0.94 (0.58 - 1.54) | 16 | 1.21 (0.66 - 2.20) | 0.76 |
| <i>P</i> _{homogeneity} ⁴ | | 0.99 | | 0.76 | |
| Average daily dose (DDD) | | | | | |
| Never exposed to statins | | ref | | ref | |
| < 1 | 51 | 0.99 (0.72 - 1.35) | 46 | 1.28 (0.91 - 1.80) | 0.27 |
| ≥ 1 | 7 | 0.75 (0.35 - 1.60) | 18 | 2.42 (1.47 - 3.98) | 0.01 |
| <i>P</i> _{trend} | | 0.43 | | 0.02 | |
| <i>P</i> _{homogeneity} | | 0.51 | | 0.04 | |

Abbreviations: CI: confidence interval; DDD: defined daily dose; HR: hazard ratio; UVR: ultraviolet radiation.

¹ Number of cases ever exposed to statins.

² Model with exposure lagged by one year, stratified by year of birth and adjusted for age (time scale), residential UVR exposure at birth and at inclusion, pigimentary traits, and family history of skin cancer.

³ P for homogeneity of the HRs across residential UVR exposure strata.

⁴ P for homogeneity of the HRs across pigimentary trait strata.

Table S3. Associations between statin exposure (vs. non exposure) and melanoma risk according to anatomic site and histologic type, E3N cohort (n= 62,473), France, 2004-2014

| | Never use of statins | No. exposed cases | Ever use of statins HR ^{1,2} (95% CI) |
|--|----------------------|-------------------|---|
| Anatomic site of melanoma (No. cases) | | | |
| Trunk (n=46) | ref | 9 | 0.93 (0.44 - 1.98) |
| Head and neck (n=63) | ref | 16 | 0.98 (0.55 - 1.75) |
| Upper limbs (n=74) | ref | 11 | 0.57 (0.29 - 1.08) |
| Lower limbs (n=143) | ref | 40 | 1.39 (0.95 - 2.02) |
| <i>p</i> homogeneity across sites | | | 0.13 |
| Histologic type of melanoma (No. cases) | | | |
| SSM (n=210) | ref | 48 | 1.04 (0.75 - 1.45) |
| NM (n=9) | ref | 2 | 0.81 (0.16 - 3.95) |
| LMM (n=58) | ref | 13 | 0.82 (0.44 - 1.55) |
| ALM (n=7) | ref | 1 | 0.67 (0.08 - 5.86) |
| Other (n=53) | ref | 16 | 1.45 (0.79 - 2.66) |
| <i>p</i> homogeneity across types | | | 0.75 |

Abbreviations: ALM: acro-lentiginous melanoma; CI: confidence intervals; HR: hazard ratio; LMM: lentigo maligna melanoma; NM: nodular melanoma; SSM: superficial spreading melanoma.

¹ Competing-risk models with exposure lagged by one year, stratified by year of birth and adjusted for age (time scale), residential UVR exposure at birth and at inclusion, pigmentary traits, and family history of skin cancer. N= 129 melanoma cases with missing location were excluded for site analyses; and N=118 melanoma cases with missing histological type were excluded for type analyses.

² Excluding the 188 skin cancer cases of unknown type.

Table S4. Associations between statin exposure (vs. non exposure) and BCC risk according to anatomic site, E3N cohort (n= 62,473), France, 2004-2014

| | Never use of statins | No. exposed cases | Ever use of statins HR ^{1,2} (95% CI) |
|--|----------------------|-------------------|---|
| Anatomic site of BCC (No. cases) | | | |
| Trunk (n=180) | ref | 34 | 0.80 (0.54 - 1.17) |
| Head and neck (n=759) | ref | 171 | 1.01 (0.84 - 1.20) |
| Upper limbs (n=79) | ref | 10 | 0.52 (0.26 - 1.02) |
| Lower limbs (n=71) | ref | 16 | 1.05 (0.59 - 1.87) |
| <i>p</i> homogeneity across sites | | | 0.22 |

Abbreviations: BCC: basal-cell carcinoma; CI: confidence intervals; HR: hazard ratio.

¹ Competing-risk models with exposure lagged by one year, stratified by year of birth and adjusted for age (time scale), residential UVR exposure at birth and at inclusion, pigmentary traits, and family history of skin cancer. N= 652 BCC cases with unknown anatomic site were excluded for site analyses.

² Excluding the 188 skin cancer cases of unknown type.

Table S5. Associations between statin exposure and skin cancer risk: model with exposure lagged by two years, E3N cohort (n= 62,473), France, 2004-2014

| | Melanoma | | BCC | | SCC | |
|--|-----------|----------------------------|-----------|----------------------------|-----------|----------------------------|
| | No. cases | HR ^{1,2} (95% CI) | No. cases | HR ^{1,2} (95% CI) | No. cases | HR ^{1,2} (95% CI) |
| Statin exposure | | | | | | |
| Never | 356 | ref | 1422 | ref | 217 | ref |
| Ever | 99 | 1.05 (0.83 - 1.32) | 319 | 0.87 (0.77 - 0.99) | 51 | 0.85 (0.62 - 1.17) |
| Cumulative number of DDDs | | | | | | |
| Never exposed | 356 | ref | 1422 | ref | 217 | ref |
| < 300 DDD | 27 | 1.16 (0.78 - 1.72) | 79 | 0.86 (0.69 - 1.08) | 12 | 0.83 (0.46 - 1.49) |
| ≥ 300 - < 900 DDD | 18 | 0.97 (0.60 - 1.57) | 69 | 0.98 (0.76 - 1.25) | 4 | 0.36 (0.13 - 0.96) |
| ≥ 900 DDD | 31 | 1.24 (0.85 - 1.82) | 75 | 0.77 (0.60 - 0.97) | 17 | 1.01 (0.61 - 1.70) |
| Unknown | 23 | 0.85 (0.56 - 1.31) | 96 | 0.90 (0.73 - 1.11) | 18 | 1.02 (0.63 - 1.67) |
| <i>P</i> _{trend} ³ | | 0.36 | | 0.71 | | 0.52 |
| Cumulative duration of exposure (years) | | | | | | |
| Never exposed | 356 | ref | 1422 | ref | 217 | ref |
| < 1 year | 24 | 1.18 (0.78 - 1.79) | 71 | 0.89 (0.70 - 1.13) | 10 | 0.80 (0.42 - 1.51) |
| ≥ 1- < 3 years | 20 | 1.05 (0.66 - 1.65) | 65 | 0.89 (0.69 - 1.14) | 9 | 0.79 (0.40 - 1.54) |
| ≥ 3 years | 33 | 1.10 (0.76 - 1.60) | 94 | 0.81 (0.65 - 1.01) | 19 | 0.99 (0.60 - 1.62) |
| Unknown | 22 | 0.89 (0.58 - 1.38) | 89 | 0.91 (0.73 - 1.13) | 13 | 0.79 (0.45 - 1.40) |
| <i>P</i> _{trend} ³ | | 0.55 | | 0.77 | | 0.62 |
| Average daily dose (DDD) | | | | | | |
| Never exposed | 356 | ref | 1422 | ref | 217 | ref |
| < 1DDD | 80 | 1.01 (0.79 - 1.30) | 270 | 0.88 (0.77 - 1.01) | 43 | 0.86 (0.62 - 1.21) |
| ≥ 1DDD | 19 | 1.24 (0.78 - 1.97) | 49 | 0.81 (0.61 - 1.08) | 8 | 0.80 (0.39 - 1.63) |
| <i>P</i> _{trend} ³ | | 0.45 | | 0.64 | | 0.96 |
| Time since first exposure (years) | | | | | | |
| Never exposed | 356 | ref | 1422 | ref | 217 | ref |
| < 4 years | 37 | 1.12 (0.80 - 1.58) | 118 | 0.93 (0.77 - 1.12) | 12 | 0.61 (0.34 - 1.10) |
| ≥ 4 years | 40 | 0.96 (0.68 - 1.36) | 131 | 0.84 (0.69 - 1.01) | 29 | 1.14 (0.75 - 1.74) |
| Unknown | 22 | 1.09 (0.71 - 1.69) | 70 | 0.85 (0.67 - 1.09) | 10 | 0.72 (0.38 - 1.36) |
| <i>P</i> _{trend} ³ | | 0.60 | | 0.49 | | 0.10 |
| Age at first exposure (years) | | | | | | |
| Never exposed | 356 | ref | 1422 | ref | 217 | ref |
| < 60 years old | 28 | 1.27 (0.85 - 1.90) | 85 | 1.03 (0.82 - 1.29) | 10 | 1.06 (0.54 - 2.07) |
| ≥ 60 years old | 39 | 0.98 (0.69 - 1.38) | 135 | 0.88 (0.73 - 1.05) | 15 | 0.56 (0.33 - 0.96) |
| Unknown | 32 | 0.97 (0.67 - 1.41) | 99 | 0.76 (0.61 - 0.94) | 26 | 1.07 (0.70 - 1.64) |
| <i>P</i> _{trend} ³ | | 0.26 | | 0.32 | | 0.76 |
| Type (ever exposure vs. never) | | | | | | |
| Atorvastatin | 33 | 0.99 (0.69 - 1.42) | 101 | 0.81 (0.66 - 0.99) | 22 | 1.12 (0.72 - 1.74) |
| Simvastatin | 33 | 1.31 (0.92 - 1.88) | 88 | 0.93 (0.75 - 1.16) | 10 | 0.61 (0.32 - 1.16) |
| Pravastatin | 32 | 1.02 (0.71 - 1.47) | 112 | 0.95 (0.78 - 1.16) | 16 | 0.80 (0.48 - 1.33) |
| Fluvastatin | 10 | 1.10 (0.58 - 2.07) | 32 | 0.97 (0.68 - 1.38) | 4 | 0.72 (0.26 - 1.94) |
| Rosuvastatin | 15 | 0.76 (0.45 - 1.29) | 61 | 0.92 (0.70 - 1.19) | 12 | 1.21 (0.66 - 2.21) |
| <i>P</i> _{homogeneity} | | 0.55 | | 0.80 | | 0.46 |
| Lipophilicity⁴ | | | | | | |
| Never exposed | 356 | ref | 1422 | ref | 217 | ref |
| Lipophilic | 58 | 1.19 (0.89 - 1.58) | 162 | 0.86 (0.73 - 1.01) | 26 | 0.84 (0.56 - 1.27) |
| Hydrophilic | 29 | 0.92 (0.63 - 1.35) | 112 | 0.90 (0.74 - 1.09) | 16 | 0.79 (0.47 - 1.33) |
| Lipophilic and hydrophilic | 12 | 0.87 (0.49 - 1.55) | 45 | 0.85 (0.63 - 1.15) | 9 | 1.05 (0.53 - 2.07) |
| <i>P</i> _{homogeneity} | | 0.45 | | 0.93 | | 0.80 |

Abbreviations: BCC: basal-cell carcinoma; CI: confidence intervals; DDD: defined daily dose; HR: hazard ratio; SCC: squamous-cell carcinoma.

¹ Model stratified by year of birth and adjusted for age (time scale), residential UVR exposure at birth and at inclusion, pigmentary traits, and family history of skin cancer.

² Excluding the 188 skin cancer cases of unknown type.

³ Among exposed women with known characteristics of exposure.

⁴Lipophilic statins include atorvastatin, simvastatin and fluvastatin while hydrophilic statins include rosuvastatin and pravastatin

Table S6. Associations between statin exposure and skin cancers risks, E3N cohort (n= 48,933), France, new user design, 2006-2014

| | Melanoma | | BCC | | SCC | |
|--|-----------|----------------------------|-----------|----------------------------|-----------|----------------------------|
| | No. cases | HR ^{1,2} (95% CI) | No. cases | HR ^{1,2} (95% CI) | No. cases | HR ^{1,2} (95% CI) |
| Statin exposure | | | | | | |
| Never | 288 | ref | 1121 | ref | 167 | ref |
| Ever | 35 | 1.18 (0.83 - 1.69) | 102 | 0.88 (0.72 - 1.08) | 14 | 0.79 (0.46 - 1.39) |
| Cumulative number of DDDs | | | | | | |
| Never exposed | 288 | ref | 1121 | ref | 167 | ref |
| < 300 DDD | 21 | 1.38 (0.88 - 2.16) | 53 | 0.89 (0.67 - 1.17) | 9 | 1.01 (0.52 - 1.99) |
| ≥ 300 - < 900 DDD | 9 | 0.82 (0.42 - 1.60) | 38 | 0.90 (0.65 - 1.25) | 4 | 0.62 (0.23 - 1.68) |
| ≥ 900 DDD | 5 | 1.45 (0.59 - 3.55) | 11 | 0.80 (0.44 - 1.45) | 1 | 0.43 (0.06 - 3.09) |
| <i>P</i> _{trend} ³ | | 0.52 | | 0.84 | | 0.52 |
| Cumulative duration of exposure (years) | | | | | | |
| Never exposed | 288 | ref | 1121 | ref | 167 | ref |
| < 1 year | 17 | 1.32 (0.81 - 2.16) | 44 | 0.87 (0.64 - 1.17) | 8 | 1.04 (0.51 - 2.12) |
| ≥ 1 - < 3 years | 11 | 0.95 (0.51 - 1.74) | 40 | 0.89 (0.65 - 1.22) | 5 | 0.73 (0.30 - 1.79) |
| ≥ 3 years | 7 | 1.38 (0.65 - 2.97) | 18 | 0.92 (0.57 - 1.47) | 1 | 0.31 (0.04 - 2.27) |
| <i>P</i> _{trend} ³ | | 0.44 | | 0.68 | | 0.12 |
| Average daily dose (DDD) | | | | | | |
| Never exposed | 288 | ref | 1121 | ref | 167 | ref |
| < 1 DDD | 29 | 1.12 (0.76 - 1.65) | 91 | 0.90 (0.73 - 1.12) | 13 | 0.86 (0.48 - 1.53) |
| ≥ 1 DDD | 6 | 1.65 (0.73 - 3.72) | 11 | 0.75 (0.41 - 1.36) | 1 | 0.40 (0.06 - 2.87) |
| <i>P</i> _{trend} ³ | | 0.96 | | 0.57 | | 0.91 |
| Time since first exposure (years) | | | | | | |
| Never exposed | 288 | ref | 1121 | ref | 167 | ref |
| < 4 years | 29 | 1.28 (0.87 - 1.88) | 81 | 0.92 (0.73 - 1.15) | 10 | 0.76 (0.40 - 1.45) |
| ≥ 4 years | 6 | 0.86 (0.38 - 1.96) | 21 | 0.76 (0.49 - 1.19) | 4 | 0.90 (0.33 - 2.48) |
| <i>P</i> _{trend} ³ | | 0.72 | | 0.21 | | 0.82 |
| Age at first exposure (years) | | | | | | |
| Never exposed | 288 | ref | 1121 | ref | 167 | ref |
| < 60 years old | 7 | 1.87 (0.87 - 4.03) | 11 | 0.84 (0.46 - 1.53) | 2 | 1.36 (0.33 - 5.65) |
| ≥ 60 years old | 28 | 1.08 (0.72 - 1.61) | 91 | 0.89 (0.71 - 1.11) | 12 | 0.74 (0.41 - 1.35) |
| <i>P</i> _{trend} ³ | | 0.72 | | 0.21 | | 0.82 |
| Type (Ever exposure) | | | | | | |
| Never exposed | 288 | ref | 1121 | ref | 167 | ref |
| Atorvastatin | 9 | 0.98 (0.50 - 1.91) | 28 | 0.87 (0.59 - 1.26) | 4 | 0.80 (0.29 - 2.17) |
| Simvastatin | 9 | 1.35 (0.69 - 2.64) | 16 | 0.64 (0.39 - 1.05) | 3 | 0.84 (0.27 - 2.64) |
| Pravastatin | 7 | 1.08 (0.51 - 2.29) | 28 | 1.20 (0.82 - 1.75) | 2 | 0.55 (0.14 - 2.23) |
| Fluvastatin | 4 | 2.61 (0.96 - 7.07) | 4 | 0.72 (0.27 - 1.92) | 0 | – |
| Rosuvastatin | 12 | 0.97 (0.54 - 1.75) | 40 | 0.93 (0.67 - 1.28) | 6 | 1.00 (0.44 - 2.29) |
| <i>P</i> _{homogeneity} | | 0.50 | | 0.37 | | 0.91 |
| Lipophilicity⁴ | | | | | | |
| Never exposed | 288 | ref | 1121 | ref | 167 | ref |
| Lipophilic | 18 | 1.42 (0.88 - 2.30) | 39 | 0.79 (0.57 - 1.08) | 7 | 0.91 (0.42 - 1.95) |
| Hydrophilic | 13 | 0.95 (0.54 - 1.66) | 55 | 1.02 (0.78 - 1.34) | 7 | 0.86 (0.40 - 1.85) |
| Lipophilic and hydrophilic | 4 | 1.30 (0.48 - 3.51) | 8 | 0.68 (0.34 - 1.37) | 0 | – |
| <i>P</i> _{homogeneity} | | 0.56 | | 0.36 | | 0.93 |

Abbreviations: BCC: basal-cell carcinoma; CI: confidence interval; DDD: defined daily dose; HR: hazard ratio; SCC: squamous-cell carcinoma.

¹ Model with exposure lagged by one year, stratified by year of birth and adjusted for age (time scale), residential UVR exposure at birth and at inclusion, pigmentary traits, and family history of skin cancer.

² Excluding the 188 skin cancer cases of unknown type.

³ Among exposed women, using the exact values of the considered parameter as a continuous variable.

⁴ Lipophilic statins include atorvastatin, simvastatin and fluvastatin while hydrophilic statins include rosuvastatin and pravastatin.