Statin use is not associated with reduced risk of skin cancer: a meta-analysis

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Background: There is contradictory evidence about the association between statin and skin cancer.

Methods: Literature search in PubMed and Web of Science was undertaken up to June 2013. Pooled relative risk (RR) estimates and 95% confidence intervals (CIs) were calculated.

Result: A total of 21 articles with 29 studies were identified. No association was found between statin and skin cancer among neither melanoma (RR, 0.94; 95% CI, 0.85–1.04) nor non-melanoma skin cancer (RR, 1.03; 95% CI, 0.90–1.19).

Conclusion: Our meta-analysis does not support a potential role of statin use in the prevention of skin cancer.

Skin cancer is one of the most common cancers, which is divided into two major groups, melanoma and non-melanoma skin cancers (NMSCs). Melanoma is the major cause of death from skin cancer (Society, 2013) and considered as one of the most therapy-resistant malignancies (Gogas et al, 2013). If left untreated, NMSCs also can become destructive, invading local tissues and causing disfigurement (Miller et al, 2010).

Statins, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors have received increasing attention owing to their possible anticancer effects (Sarrabayrouse et al, 2007; Coimbra et al, 2010; Zhang et al, 2011). According to a meta-analysis of 16 randomized control trials (RCTs) before 2009 (Bonovas et al, 2010), no association was found between statins and melanoma. Several observational studies also presented that statins have not identified anticancer effects (Marelli et al, 2011; Leung et al, 2013). However, other recent observational studies showed that statins may be associated with a lower risk of melanoma (Haukka et al, 2010; Jacobs et al, 2011). Thus, the effect of statins on the skin cancer risk remains to be determined.

MATERIALS AND METHODS

Selection criteria. The studies considered in this meta-analysis were RCTs, case–control or cohort studies that evaluated exposure to statins and risk of skin cancer (including melanoma and NMSCs). The following inclusion criteria had to be fulfilled: (1) clearly defined and evaluated exposure to statins; (2) skin cancer incidence as the outcome of interest; (3) reported RR or odds ratio (OR) with 95% CI or provided data for their calculation. Studies reporting different measures of RR such as risk ratio, rate ratio, hazard ratio and OR were included because in practice they yield a similar RR estimate, given the absolute risk of skin cancer is low.

Identifying studies. Broad searches were conducted to identify all published literatures and meeting abstracts in Pubmed (-2013) and Web of Science (1985–2013) limited to those human subjects without limitation on language. Search terms included 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA reductase inhibitor), statin, atorvastatin, cerivastatin, fluvastatin, lovastatin, mevastatin, pravastatin, pitavastatin, rivastatin, rosuvastatin, simvastatin, combined with melanoma or non-melanoma or cancer or neoplasm or malignancy. Flow diagram is shown in Supplementary Figure 1. The detail of data collection is shown in Supplementary Material 1.

Quality assessment. The criteria adapted from the Cochrane handbook for systematic reviews of interventions (Higgins et al, 2011) and the validated Newcastle–Ottawa scale (NOS) (Wells et al, 2000) were used to assess the methodological quality of RCTs, case–control and cohort studies, respectively.

Statistical analysis. Study-specific risk estimates were extracted from each article, and log risk estimates were weighted by the
Table 1. Characteristics of included studies assessing the risk of skin cancer with statin use

| Author, year | Statin type | Study design | Study quality | Location | Time period | Outcome assessment | Duration from statin treatment start and diagnosis |
|--------------|-------------|--------------|---------------|----------|-------------|-------------------|-----------------------------------------------|
| Leung et al (2013) | a, f, pr, r, s | Case–control | High | Taiwan | Recruitment from 01 January 2000 to 31 December 2008 | Investigated with the corresponding ICD-9-CM codes | Statin continuously used for at least 6 months before the index date (date of diagnosis and equivalent date for controls). |
| Koomen et al (2007) | a, c, f, pr, r, s | Case–control | High | Netherlands | Recruitment from 01 January 1991 to 14 December 2004 | The researchers extracted and recorded diagnosis and date of primary CM | One or more statins for at least 6 months of cumulative prescription duration in the 3 years before CM. |
| Kaye and Jick (2004) | NR | Case–control | High | The United States | Recruitment from 1990 to 2002 | NR | Received a prescription for a statin within the year before the index date, and their first prescription was recorded more than a year before the index date. |
| Haukka et al (2010) | a, c, f, l, pr, r, s | Case–control | High | Finland | Recruitment from 01 January 1996 to 31 December 2005 | Obtained from Finnish cancer registry | At least one prescription of any statin between 1 January 1996 and 31 Dec 2005 and had no cancer diagnosis at the date of first purchase. |
| Frohlich et al (2012) | s | Case–control | Moderate | Switzerland | 1985–2007; follow-up was performed until December 2010 | Defined as the detection of any malignant tumor | Statin therapy was initiated, usually 3–12 months after transplantation in patients who receive transplants after 1995 until the occurrence of malignancy or the end of the follow-up period. |
| Farwell et al (2008) | a, f, l, pr, s | Cohort | Moderate | The United States | Recruitment from 01 January 1997 to 31 December 2005 | A physician blinded to medication use reviewed 300 random charts with a new ICD-9-CM code for cancer from patients who were included in our analyses. | Beginning 2 years after his or her entry date and continuing until the first occurrence of the first appearance of cancer, 1 year after the last date that a prescription was filled for a medication of interest, death or the end of the analysis period. |
| Cunil-Lewandrowski et al (2011) | a, f, l, pr, r, s | Case–control | High | The United States | Recruitment from 15 March 2004 to 18 June 2007; follow-up begin from 1997 end in 2007 | Telephone questionnaire | Taking the drug at least once weekly within a year preceding the interview. |
| Karp et al (2008) | a, l, s (exclude c, pr, r) | Cohort | Moderate | Canada | Recruitment from 01 April 1998 to 31 March 2004; follow-up through 31 March 2005 | Hospitalization with cancer | Followed from hospital discharge until the occurrence of the study outcome, end of follow-up (31 March 2005). |
| Jacobs et al (2011) | f, l, pr, s | Cohort | High | The United States | Recruitment from 1992 to 1993; follow-up begin from 1997 end in 2007 | Self-administrated questionnaire | Questionnaire asked participants to report whether they had taken any cholesterol-lowering drugs regularly during the past year. |
| Marelli et al (2011) | NR | Cohort (retrospective) | High | The United States | Recruitment from 01 January 1990 to 28 February 2009 | Diagnosis of cancer recorded in the medical record after time zero | Time zero was defined as the point at which patients began to take statins or, if never on statins, the date of the first recorded low-density lipoprotein or total cholesterol level in the database. |
inverse of their variances to obtain a pooled risk estimate. Heterogeneity was assessed by using Cochrane Q statistic and estimating $I^2$ (Higgins et al, 2003). A fixed-effect model (Mantel–Haenszel) was used to calculate the pooled ORs when the test for heterogeneity was not statistically significant ($P > 0.10$), otherwise the random-effect model (DerSimonian and Laird) was employed (Song et al, 2001). Evidence of publication bias was determined using funnel plot and Egger’s statistical test (Egger et al, 1997).

Subgroup analyses were carried out by quality of study methodology, study design and duration of statin use. Sensitivity analyses were conducted to evaluate the robustness of meta-analysis results (Trikalinos et al, 2006). Cumulative meta-analysis was conducted to identify the change in trend of reporting risk over time.

Statistical analyses were performed using STATA 12.0 (STATA Corporation, College Station, TX, USA).

### RESULTS

#### Characteristics of included studies
A total of 21 articles with 29 studies were identified, among which 24 studies focused on melanoma, whereas 14 studies reported NMSCs and 3 studies did not specify the classification of skin cancer (Table 1).

With respect to melanoma, 17 studies were post-hoc analyses or RCTs, 5 were case–control studies, and 2 were cohort studies.

**Table 1.** (Continued)

| Author, year | Statin type | Study design | Study quality | Location | Time period | Outcome assessment | Duration from statin treatment start and diagnosis |
|--------------|-------------|--------------|---------------|----------|-------------|-------------------|-----------------------------------------------|
| Vinogradova et al (2011) | a, c, f, pr, r, s | Nested case–control | High | The United Kingdom | 01 January 1998–01 January 2008 | NR | At least 2 prescriptions in the 60-month period (or the 98-month period for the 10-year analysis) |
| Officers et al (2002) | pr | RCT follow-up | | Australia and New Zealand | Recruitment from April 1990 to December 1992 | All deaths and AM1 are reviewed by the outcome assessment committee | Supplies of open label pravastatin were provided to patients for a mean of 2 years beyond the end of the RCT. |
| Stegnayr et al (2005) | a | RCT | Sweden | Enrolled from February 1998 | Adverse event reporting | Safety analysis was performed after 6 months and again after 2 years. |
| Shepherd et al (1995) | pr | RCT | Scotland | Recruitment 01 February 1989 to 30 September 1991 | Based on subjects recall, further information was obtained from hospital records | 5 years. |
| Sacks et al (1996) | pr | RCT | Canada and the United States | Recruitment from 04 December 1989 to 31 December 1991 ended between 01 January 1996 and 14 February 1996 | NR | The median duration of follow-up was 5.0 years. |
| Jagtap et al (2012) | a, c, f, l, pr, r, s | RCT | The United States | Recruitment 01 October 1993 to 31 December 1998; follow-up through 20 September 2010 | Centrally adjudicated and SEER-coded cases | Cancer diagnoses were updated in the observational study or semiannually in the RCT by mail and/or telephone questionnaires. |
| Heart Protection Study Collaborative G (2005) | s | RCT | The United Kingdom | Recruitment from July 1994 to May 1997 | Question participants and review the calendar-packed tablets remaining | Mean duration of follow-up was 5.0 years. |
| GISSI (2000) | pr | RCT | Italy | Recruitment from October 1993 to September 1995 | NR | 23 months |
| Downs et al (1998) | l | RCT | The United States | Recruitment from 30 May 1990 to 12 February 1993 | NR | At least 5 years of follow-up. |
| Strandberg et al (2004) | s | RCT follow-up | Denmark, Finland, Iceland, Norway, Sweden | Recruitment from 19 May 1988 to 16 August 1989 follow-up end at 01 August 1994 | Classified by an independent end point committee with hospital records | A 2-year, interim follow-up study. |
| Stein et al (2006) | f | 8 RCTs (post hoc analyses) | Multicenter | NR | NR | NR |

Abbreviations: CM = cutaneous melanoma; NR = not reported; RCT = randomized control trial. NOS score into three levels (high quality, score $\geq 7$; moderate quality, 4 $< $ score $< 7$; low quality, score $< 4$).
A total of 8433 cases of melanoma were cumulatively reported in 414,627 patients, and 1,147,088 individuals were classified as statin users. Concerning the NMSCs, 12 studies were post-hoc analyses or RCTs, 1 was case-control study and 1 was cohort study, of which 3354 cases and 99,906 controls were eligible.

**Quality assessment results.** The qualities of studies were moderate to high (Table 1).

**Melanoma.** The association between statins and melanoma risk was not statistically significant assuming a random-effect model (RR, 0.94; 95% CI, 0.85–1.04). However, moderate heterogeneity was observed ($P = 0.07 < 0.1$; $I^2 = 33.8\%$). The funnel plot was symmetric and no publication bias was observed using Egger’s test ($P = 0.95$).

Subgroup analysis (see Supplementary Table 1) represented that none of the stratifications (study design, location and study duration) could account for the heterogeneity observed in the overall analysis. Regarding long-term statin use in particular, the results did not materially change (RR, 0.93; 95% CI, 0.73–1.18). Cumulative meta-analysis showed no significant change in trend of reporting risk from positive to negative.

**NMSCs.** The statin use with increased NMSCs was not statistically significant no matter assuming a fixed-effect model (RR, 1.12; 95% CI, 0.90–1.37) or a random-effect model (RR, 1.03; 95% CI, 0.90–1.19). The Cochran’s Q-test had a $P$-value of 0.007, and $I^2$ was 61.7%, indicating there was moderate heterogeneity within the group. The $P$ values for the Egger’s test were 0.16, showing no evidence of publication bias.

Subgroup analysis showed that the results were not substantially changed by study design. In the sensitivity analysis, we identified the study by Stein et al (2006) and Haukka et al (2010) contributed most to the between-study variability.

**RR estimates and 95% CIs are listed in Tables 2 and 3.**

**DISCUSSION**

There are debates regarding the association between statin use and skin cancer.

One view is that the immunomodulatory effects of statins may impair the host antitumor immune response by suppressing tumor-specific effector T-cell response, therefore leading to an increased cancer risk (Goldstein et al, 2009). Notably, immunosuppression represents an emerging risk factor for NMSCs. The immunomodulatory pleiotropic actions of statins resemble the immune phenotype, which predicts risk for post-transplantation NMSCs (Mausner-Fainberg et al, 2008; Carroll et al, 2010; Mascielli and Goldstein, 2013). In addition, immunosuppressive actions of statin therapy may in part be related to increasing risk of a rare and aggressive neuroendocrine skin cancer, Merkel cell carcinoma (Kaae et al, 2010; Sahi et al, 2012).

On the contrary, in several in vitro and in vivo pre-clinical models of melanoma, statins have been presented to involve in anticancer activity (Sarrabayrouse et al, 2007; Coimbra et al, 2010; Ivanov and Hei, 2011). They may have anticancer effects through targeting on HMGCR and the mevalonate pathway, which have a

| Author, year | Duration | RR Low CI | High CI | Melanoma Total | Melanoma Total | Melanoma Total |
|---------------|----------|-----------|---------|-----------------|-----------------|----------------|
| Jagtap et al (2012) | Long | 1.14 0.91 1.43 | 1200 119726 | 89 8824 | 1111 110902 |
| Marelli et al (2011) | Short | 1.08 0.85 1.37 | 259 10309 | 136 5215 | 123 5094 |
| Jacobs et al (2011) | Short | 0.79 0.66 0.96 | 3249 16 364 433 | 2108 2816 | 14 256 |
| Jacobs et al (2011) | Short | 0.89 0.75 1.06 | 400 1000 | 109 276 | 291 724 |
| Jacobs et al (2011) | Former | 0.64 0.46 0.89 | 414627 | 805 | 90 |
| Curiel-Lewandrowski et al (2011) | Short | 0.97 0.73 1.29 | 1251 133255 | 411 28950 | 840 104305 |
| Curiel-Lewandrowski et al (2011) | Short | 1.12 0.79 1.6 | 1251 133255 | 411 28950 | 840 104305 |
| Curiel-Lewandrowski et al (2011) | Long | 0.84 0.48 1.48 | 1251 133255 | 411 28950 | 840 104305 |
| Stein et al (2006) | Short | 0.40 0.10 1.55 | 10 6801 | 3 3512 | 7 3289 |
| Heart Protection Study Collaborative G (2005) | Long | 1.66 0.78 3.54 | 27 20536 | 17 10269 | 10 10267 |
| Stegnayr et al (2005) | Short | 0.35 0.01 8.39 | 1 143 | 0 70 | 1 73 |
| GISSI (2000) | Short | 0.33 0.01 8.16 | 1 4271 | 0 2138 | 1 2133 |
| Downs et al (1998) | Long | 0.52 0.27 0.99 | 41 6605 | 14 3304 | 27 3301 |
| Sacks et al (1996) | Long | 1.33 0.30 5.94 | 7 4159 | 4 2081 | 3 2078 |
| Shepherd et al (1995) | Long | 0.67 0.19 2.35 | 10 6595 | 4 3302 | 6 3293 |
| Farwell et al (2008) | NR | 0.84 0.7 1.02 | 540 62842 | 304 37248 | 236 25594 |
| Kaye and Jick (2004) | NR | 2.5 0.8 7.3 | 26 459 | 7 79 | 19 380 |
| Koome et al (2007) | Short | 0.98 0.78 1.2 | 1318 8104 | 96 599 | 1222 7505 |
| Strandberg et al (2004) | Long | 1.29 0.48 3.45 | 16 4444 | 9 2221 | 7 2223 |
| Officers et al (2002) | Short | 1.08 0.69 1.7 | 77 9014 | 39 4512 | 38 4502 |
| Vinogradova et al (2011) | Short | 1.04 0.87 1.23 | 3249 16364 | 433 2108 | 2816 14256 |

Abbreviations: CI = confidence interval; NR = not reported; RR = relative risk.
role in the metabolic reprogramming of cancer (Clendening et al., 2010; Clendening and Penn, 2012).

This meta-analysis showed no evidence that statin use is associated with a substantially decreased or increased risk of skin cancer (neither melanoma nor NMSCs). The results were not significantly affected by study design, study location and long-term statin use, which reinforce our confidence in the validity of the conclusion. Our findings are in line with recent meta-analyses on the association between statin use and melanoma (Freeman et al., 2006; Bonovas et al., 2010). However, unlike in vitro and animal studies, meta-analyses do not demonstrate an effect of statins in humans, it is possible because of the inconsistent dosage and drug concentrations, some malignant cell lines are not inhibited by the same concentrations of statins achieved in humans (Freeman et al., 2006).

Moderate heterogeneity was identified in our meta-analysis, which should be considered with caution. There may be several factors contributing to the heterogeneity. The first reason is the multiple criteria for the diagnosis of skin cancer, which may introduce spectrum-of-disease bias. Second, detailed information for the type of statins was not provided, which made it hard to further investigate the potential difference between lipophilic and hydrophilic statins.

There could be several potential limitations in this meta-analysis. First, skin cancer (melanoma or NMSCs) was not the primary end point of the included RCTs; we were not able to obtain primary data regarding skin cancer diagnosis for all study participants. Second, even though the included studies had acceptable quality, detailed information of confounding factors was not provided (such as family history, skin color and sun exposure). To minimize the risk of misleading conclusions led by the lack of confounder control, we extracted adjusted RRs for different confounding factors whenever available. The third aspect deals with the varied definitions of drug exposure among eligible studies. Jacobs et al. (2011) divided the participants into ‘former user’, ‘current use’ and ‘no reported use’ groups, whereas in other studies, participants were identified as statin users or non-statin users.

However, the present study has several strengths. First of all, 21 articles with 29 studies were included, reporting data of 11 787 skin cancer cases. No exclusion criteria of language, location or study quality were applied. With large numbers of incident cases, meta-analysis could provide high statistical power. Moreover, no evidence of substantial publication bias was observed. Furthermore, the findings were similar in subgroup analysis of RCTs, case–control and cohort studies, although the methodological differences of original studies may introduce potential biases. In addition, even though moderate heterogeneity was observed, summary estimates were substantially unchanged after excluding the studies introducing most to the heterogeneity.

Two aspects should be noted in future studies. The potential use of statins for skin cancer prevention, especially melanoma, and the utility of testing statins as therapy in combination with chemotherapy are needed. In addition, because of the widespread use of statins, extending follow-up periods to identify potential effects on skin cancer in the longer-term statin use might be useful.

In conclusion, the meta-analysis indicates that there is no association between statin use and skin cancer risk on the basis of the findings of RCTs, case–control and cohort studies.

**CONFLICT OF INTEREST**

The authors declare no conflict of interest.

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