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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

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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	Netherland	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 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 recieve 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.
Curiel-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, f, 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.

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.
Stegmayr *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 $\geqslant 7$; moderate quality, $4 \leqslant$ score < 7; low quality, score < 4).

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.

A total of 8433 cases of melanoma were cumulatively reported in 414 627 patients, and 114 708 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, 1.05–1.20) 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; Mascitelli 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

Table 2. Summary of adjusted RRs assessing the risk of melanoma with statin exposure

					All subjects		On statins		Not on statins	
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	119 726	89	8824	1111	110 902
Marelli *et al* (2011)	Short	1.08	0.85	1.37	259	10 309	136	5215	123	5094
Jacobs *et al* (2011)					1251	133 255	411	28 950	840	104 305
Jacobs *et al* (2011)	Long	0.79	0.66	0.96						
Jacobs *et al* (2011)	Short	0.89	0.75	1.06						
Jacobs *et al* (2011)	Former	0.64	0.46	0.89						
Curiel-Lewandrowski *et al* (2011)		0.97	0.73	1.29	400	1000	109	276	291	724
Curiel-Lewandrowski *et al* (2011)	Short	1.12	0.79	1.6						
Curiel-Lewandrowski *et al* (2011)	Long	0.84	0.48	1.48						
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	20 536	17	10 269	10	10 267
Stegmayr *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	62 842	304	37 248	236	25 594
Kaye and Jick (2004)	NR	2.5	0.8	7.3	26	459	7	79	19	380
Koomen *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	16 364	433	2108	2816	14 256

Abbreviations: CI = confidence interval; NR = not reported; RR = relative risk.

Table 3. Summary of adjusted RRs assessing the risk of skin cancer (except melanoma) with statin exposure

					All subjects		On statins		Not on statins	
Author, year	Disease	RR	Low CI	High CI	Skin	Total	Skin	Total	Skin	Total
Marelli *et al* (2011)	Non-melanoma	0.98	0.81	1.19	394	10 309	197	5215	197	5094
Haukka *et al* (2010)	Non-melanoma	1.28	1.16	1.41	1735	50 294	990	25 445	745	24 849
Strandberg *et al* (2004)	Non-melanoma	1.04	0.62	1.74	57	4444	29	2221	28	2223
Frohlich *et al* (2012)	NR	0.76	0.49	1.18	61	255	32	151	29	104
Karp *et al* (2008)	NR	0.88	0.55	1.41	75	30 076	26	11 338	49	18 738
Leung *et al* (2013)	NR	1.62	0.662	3.875	88	34 205	12	6841	76	27 364
GISSI (2000)	Non-melanoma	1.00	0.06	15.94	2	4271	1	2138	1	2133
Downs *et al* (1998)	Non-melanoma	1.03	0.87	1.22	493	6605	250	3304	243	3301
Stein *et al* (2006)	Non-melanoma	0.77	0.60	1.00	228	6801	103	3512	125	3289
Stegmayr *et al* (2005)	Non-melanoma	1.20	1.00	1.45	445	20 536	243	10 269	202	10 267

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 demenstrate 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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