1-7-2016

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Recommended Citation
epub ahead of print

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FULL PAPER

BJC

British Journal of Cancer (2016), 1–7 | doi: 10.1038/bjc.2015.376

Keywords: skin cancer; non-melanoma skin cancer; statins; 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitor; HMG Co-A reductase inhibitor; basal cell carcinoma; squamous cell carcinoma; cholesterol

Relation of statin use with non-melanoma skin cancer: prospective results from the Women's Health Initiative

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Background: The relationship between statin use and non-melanoma skin cancer (NMSC) is unclear with conflicting findings in literature. Data from the Women's Health Initiative (WHI) Observational Study and WHI Clinical Trial were used to investigate the prospective relationship between statin use and NMSC in non-Hispanic white (NHW) postmenopausal women.

Methods: The WHI study enrolled women aged 50–79 years at 40 US centres. Among 133 541 NHW participants, 118 357 with no cancer history at baseline and complete medication/covariate data comprised the analytic cohort. The association of statin use (baseline, overall as a time-varying variable, duration, type, potency, lipophilicity) and NMSC incidence was determined using random-effects logistic regression models.

Results: Over a mean of 10.5 years of follow-up, we identified 11 555 NMSC cases. Compared with participants with no statin use, use of any statin at baseline was associated with significantly increased NMSC incidence (adjusted odds ratio (OR_{adj}) 1.21; 95% confidence interval (CI): 1.07–1.35)). In particular, lovastatin (OR 1.52; 95% CI: 1.08–2.16), simvastatin (OR 1.38; 95% CI: 1.12–1.69), and lipophilic statins (OR 1.39; 95% CI: 1.18–1.64) were associated with higher NMSC risk. Low and high, but not medium, potency statins were associated with higher NMSC risk. No significant effect modification of the statin–NMSC relationship was found for age, BMI, smoking, solar irradiation, vitamin D use, and skin cancer history.

Conclusions: Use of statins, particularly lipophilic statins, was associated with increased NMSC risk in postmenopausal white women in the WHI cohort. The lack of duration–effect relationship points to possible residual confounding. Additional prospective research should further investigate this relationship.

Non-melanoma skin cancer (NMSC), which includes basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), is the most common cancer in the United States and is responsible for significant economic costs (Rogers *et al*, 2010; National Cancer Institute, 2012). Although NMSC is more common among men than women, the incidence has rapidly increased for both genders

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These data were presented in part as a Late-Breaking Abstract at the 2014 Society of Investigative Dermatology meeting (LB806).

Received 21 June 2015; revised 24 September 2015; accepted 8 October 2015

(Christenson *et al*, 2005; Rogers *et al*, 2010). Well-established NMSC risk factors include ultraviolet radiation from sun or tanning bed exposure (Gallagher *et al*, 1995; van Dam *et al*, 1999), increasing age (Gray *et al*, 1997; Karagas *et al*, 1999), immunosuppression (particularly for SCCs) (Lichter *et al*, 2000), and light skin (Hussain *et al*, 2009).

In laboratory studies, statins (3-hydroxy-3 methylglutaryl coenzyme A, HMG-CoA reductase inhibitors) have appeared to protect against NMSC by causing apoptosis of keratinocytes by lowering cellular cholesterol levels (Gniadecki, 2004) and activating the RAFMEK (mitogen-activated protein kinase 1) pathway (Wu *et al*, 2004). Furthermore, cholesterol depletion because of statin use has been shown to inhibit the Hedgehog signaling pathway (Cooper *et al*, 2003; Corcoran and Scott, 2006), which is critical in the carcinogenesis of basal cell carcinoma (Tang *et al*, 2007; Von Hoff *et al*, 2009). Statins have also been shown to inhibit cancer cells in animal models and *in vitro* (Chan *et al*, 2003). However, statins also have immunomodulatory properties including increasing regulatory T cells, which may lead to an increased risk for NMSC (Curiel, 2007; Jang, 2008; Mausner-Fainberg *et al*, 2008; Goldstein *et al*, 2009a,b). Additionally, statins have been associated with increased photosensitivity, which may be due to their effect on signal-transduction pathways leading to proinflammatory cytokines (Zhang and Elmets, 2010).

Clinical studies have also reported inconsistent relationships between NMSC and statin use. Several large retrospective studies and a meta-analysis of randomised controlled trials (RCTs) found no significant relationship between statins and NMSC incidence (Bjerre and LeLorier, 2001; Asgari *et al*, 2009; Haukka *et al*, 2010; Li *et al*, 2014). An analysis of three statin RCTs designed to examine cardiovascular outcomes also found no increased risk of skin cancer incidence (Peto *et al*, 2008), whereas other studies (both observation and case–control) have found lower incidence of NMSC and/or overall skin cancer in statin users (Blais *et al*, 2000; Graaf *et al*, 2004). On the other hand, several reviews and RCTs have found an increased incidence of NMSC and/or melanoma with statin use (Scandinavian Simvastatin Survival Study Group, 1994; Collins *et al*, 2002; Kuoppala *et al*, 2008).

To contribute further to this literature, we investigated the prospective relationship between NMSC and statin use among postmenopausal white women in the Women's Health Initiative (WHI) Clinical Trial (CT) and WHI Observational Study (OS). Given the high NMSC incidence, especially in older populations, and 2013 cholesterol management guidelines, which are expected to broaden statin use to ~56 million people in the United States, including patients without known cardiovascular disease (Stone *et al*, 2014), it is important to further understand this relationship.

MATERIALS AND METHODS

Design, setting, and participants. The WHI was designed to study morbidity and mortality in postmenopausal women through a large OS and a set of CTs, including diet modification (DM), hormone therapy (HT), and calcium and vitamin D (CaD), as described previously (WHI Investigators, 1998). In brief, women were recruited between 1993 and 1998 at 40 US clinical centres with the following eligibility criteria: age 50–79 years, postmenopausal, estimated survival of at least 3 years, and no plans to move away from the recruitment area within 3 years. The combined OS + CT multiethnic cohort included 161 808 women. For our analyses, we included only white women owing to the low number of skin cancer cases in other ethnicities, which reduced the analytic cohort size to 133 541. We then excluded participants who lacked follow-up time and medication information at baseline, had personal cancer history at baseline (including NMSC and melanoma), and were missing confounders in the scientific model; this resulted in a final cohort size of 118 357 women (Figure 1).

Measurement of exposures and confounders. For measurement of statin use, participants were instructed to bring prescription medication containers to the baseline screening interview. Medication names were entered into the database by interviewers. Statin use was also updated at years 1, 3, 6, and 9 for CT participants, and year 3 for OS participants using the same methodology. OS women were followed until year 6 and CT women were followed until year 9 because of low number of medication inventories due to study closeout.

Statins were defined as any HMG-CoA reductase inhibitors, and classified based on potency and lipophilicity/hydrophilicity according to a prior WHI study on statin use and melanoma (Jagtap *et al*, 2012). Lipophilic statins included lovastatin, simvastatin, fluvastatin, and cerivastatin. Hydrophilic statins included atorvastatin, pravastatin, and rosuvastatin. Potency was defined as follows: low – lovastatin, fluvastatin; medium – pravastatin; high – simvastatin, atorvastatin, cerivastatin, rosuvastatin. A small percentage (<1%) of participants used more than one statin drug; among these participants, the analysis duration of statin use was equal to the duration for the drug used for the longest duration time.

Potential confounders were included as covariates in the scientific model and defined *a priori* based on hypothesised and established factors for NMSC development. Information on confounders was collected through baseline questionnaires, and

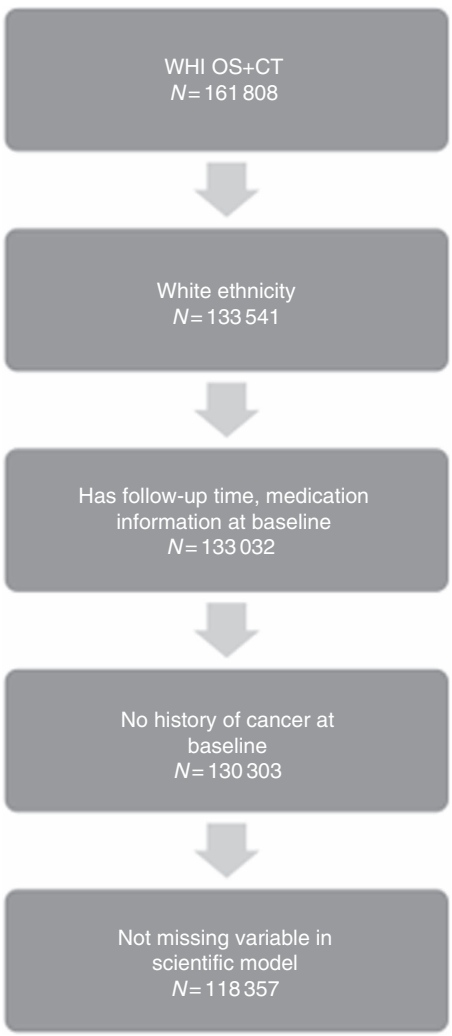

Figure 1. Sample size for WHI OS + CT analytic cohort.

Table 1A. Baseline characteristics of the WHI OS + CT cohort

	Statin use at baseline	
	No (*N* = 120 584)	Yes (*N* = 9719)
Characteristic	***N* (%)**	***N* (%)**
Age group (missing *N* = 0)		
<50–59	39 519 (32.77)	1598 (16.44)
60–69	54 232 (44.97)	5114 (52.62)
70–79 +	26 833 (22.25)	3007 (30.94)
Education (missing *N* = 836)		
<HS	4004 (3.34)	477 (4.94)
HS	20 824 (17.38)	2094 (21.69)
>HS	94 983 (79.28)	7085 (73.37)
Smoking status (missing *N* = 1562)		
Never smoked	59 758 (50.15)	4544 (47.41)
Past smoker	51 509 (43.23)	4495 (46.90)
Current smoker	7889 (6.62)	546 (5.70)
Category of vitamin D intake (dietary + supplements) (missing *N* = 250)		
<200	42 500 (35.31)	3302 (34.02)
200–<400	22 542 (18.73)	1683 (17.34)
400–<600	30 480 (25.33)	2627 (27.07)
600 +	24 826 (20.63)	2093 (21.57)
Alcohol consumption (missing *N* = 814)		
Non-drinker	30 313 (25.30)	2898 (29.98)
<1 drink per week	39 668 (33.11)	3347 (34.63)
1–<7 drinks per week	33 876 (28.27)	2378 (24.60)
7 + drinks per week	15 966 (13.32)	1043 (10.79)
BMI category (missing *N* = 1133)		
<25	45 354 (37.94)	2458 (25.50)
25–30	41 257 (34.52)	3870 (40.15)
30 +	32 920 (27.54)	3311 (34.35)
Physical activity (MET-hrs/week)		
⩽2.3	27 365 (23.91)	2257 (23.88)
>2.3–8.3	27 613 (24.13)	2473 (26.16)
>8.3–17.8	29 559 (25.83)	2504 (26.49)
>17.8	29 920 (26.14)	2219 (23.47)
Current care provider (missing *N* = 1034)		
Yes	112684 (94.20)	9508 (98.58)
No	6940 (5.80)	137 (1.42)
Hormone therapy status (missing *N* = 99)		
Never used	49.997 (41.49)	4322 (44.53)
Past user	19 214 (15.95)	1739 (17.92)
Current user	51 287 (42.56)	3645 (37.55)
Oral contraceptive use (missing *N* = 1)		
Yes	51793 (42.95)	3369 (34.66)
No	68798 (57.05)	6352 (65.34)
Langleys of exposure (missing *N* = 0)		
300–325	38 806 (32.18)	3328 (34.24)
350	25 304 (20.98)	2084 (21.44)
375–380	13 328 (11.05)	1048 (10.78)
400–430	19 130 (15.86)	1399 (14.39)
475–500	24 016 (19.92)	1860 (19.14)
Latitude region (missing *N* = 0)		
Northern (>40°N)	58 087 (48.17)	4771 (49.09)
Middle (>37–40°N)	23 045 (19.11)	1838 (18.91)
Southern (⩽37°N)	39 452 (32.72)	3110 (32.00)
Baseline NSAID use (missing *N* = 0)	46 498 (38.56)	5313 (54.67)
Skin reaction to the sun (missing *N* = 64 041)		
No change/tans but does not burn	21 963 (36.02)	2047 (38.72)
Burns, then tans	15 575 (25.54)	1183 (22.38)
Burns, tans minimally	16 499 (27.06)	1360 (25.73)
Burns, does not tan	6939 (11.38)	696 (13.17)
Daily summer sun exposure as a child (missing *N* = 62 950)		
<30 min	1457 (2.35)	128 (2.38)
30 min to 2 h	16 168 (26.09)	1433 (26.64)
>2 h	44 349 (71.56)	3818 (70.98)
Daily summer sun exposure as an adult (missing *N* = 62 906)		
<30 min	19 051 (30.73)	1905 (35.26)
30 min to 2 h	30 944 (49.91)	2610 (48.32)
>2 h	12 000 (19.36)	887 (16.42)
Sunscreen use (missing *N* = 64 647)		
None	28 541 (47.23)	2569 (49.17)
SPF 2–14	2988 (4.94)	242 (4.63)
SPF 15–24	18 308 (30.30)	1540 (29.47)
SPF 25 +	10 594 (17.53)	874 (16.73)
Calcium/Vitamin D Trial Arm		
Not randomised to CaD	92 577 (76.77	7805 (80.31
Intervention	13 978 (11.59	963 (9.91
Control	14 029 (11.63	951 (9.78
HT Trial Arm		
Not randomised to HT	100 203 (83.10)	8168 (84.04)
E-alone intervention	3686 (3.06)	301 (3.10)
E-alone control	3703 (3.07)	334 (3.44)
E + P intervention	6642 (5.51)	478 (4.92)
E + P control	6350 (5.27)	438 (4.51)
DM Trial Arm		
Not randomised to DM	83 681 (69.40)	7255 (74.65)
Intervention	14 755 (12.24)	967 (9.95)
Control	22 148 (18.37)	1497 (15.40)
OS cohort	69 189 (57.38)	6054 (62.29)

Abbreviations: BMI = body mass index; CaD = calcium and vitamin D; CT = Clinical Trial; DM = diet modification; E + P = oestrogen + progestin; HS = higher secondary; HT = hormone therapy; OS = Observational Study; WHI = Women's Health Initiative.

included the following: age group at screening (50–59, 60–69, and 70–79), education (⩽high school diploma/GED, school after high school, college degree or higher), body mass index (BMI) (<25, ⩾25–30, and >30 kg m^{-2}), smoking status (never, past, and current), vitamin D intake (<200, 200–<400, 400–<600, and ⩾600 IU), solar irradiance of region in Langleys (300–325, 350, 375–380, 400–430, and 475–500), geographic region by latitude (Southern: <35°N; Middle: 35–40°N, and Northern: >40°N), total physical activity (METs per week, quartiles), current health-care provider (yes/no, as proxy for access to medical care), adjustment for assignment to CT (active *vs* placebo arms of DM, HT conjugated equine Oestrogens and oestrogen + progestin (E + P), and calcium + vitamin D (CaD) trials) or OS, use of oral contraceptives, and use of menopausal HT.

Classification of cases (follow-up and ascertainment). Non-melanoma skin cancer cases were self-reported through questionnaires (every 6 months for CT and every year for OS) and not centrally adjudicated. Basal cell carcinoma and SCC were not reported separately. Over 10.5 average years of follow-up through August 2009, 11 555 NMSC cases were identified: 1529 among statin users and 10 026 among non-statin users.

Statistical analysis. The primary outcome of interest was development of first-ever NMSC. We used random-effects logistic regression models to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for NMSC incidence in relation to statin use, as time to diagnosis data was not available for self-

reported data. A random-effects model allows us to appropriately model the correlation between women's repeated NMSC reports. We fit two models, age- and study-arm-adjusted and multivariable-adjusted, which adjusted for the confounders listed above. We fit several models estimating ORs for NMSC as a function of these parameters of statin use separately: (1) any statin use, (2) type of statin (as defined earlier in the Materials and Methods section), (3) statin potency, (4) statin category, and (5) duration of statin use in years (none, <1, 1 to <3, $\geqslant 3$, <5, and $\geqslant 5$). The primary exposure of interest was any statin use, and all others were considered of secondary interest. As such, all secondary *P*-values were adjusted using the Bonferroni correction to control the family-wise error rate. Each *P*-value was multiplied by a factor of 4 to account for the four secondary exposures. All tests were two-sided and tested at the 0.05 level of significance.

In the primary model with any statin use as the exposure, we formally tested for effect modification in separate models for each potential effect modifier by using a Wald test to obtain an omnibus *P*-value for the statistical interaction term. We tested six prespecified variables: age (50–59, 60–69, 70–79 years), BMI (<25, $\geqslant 25$–30, and $\geqslant 30\,kg\,m^{-2}$), smoking (never, former, and current), solar irradiance Langleys ($\leqslant 375$ and >375), and vitamin D intake (<400 and $\geqslant 400$ IU).

As a *post hoc* sensitivity analysis, we analysed the relationship between NMSC and statin use at baseline using propensity score matching (PSM). Variables included for matching in the propensity score were defined *a priori* based on factors that may affect a participant's propensity for using statins, but were not likely to be affected by statin use itself: health status, age, access to regular medical, current health-care provider, recent pap smear, recent mammogram, income, occupation, education, marital status, physical activity, smoking, vitamin D use, use of oral contraceptives, use of postmenopausal hormonal therapy, solar irradiance in Langleys, latitude, US region, family history (skin cancer, other cancer, MI, diabetes, stroke), osteoporosis history, arthritis history, multivitamin use, history of fracture before the age of 55 years, and CT arms. Propensity was determined by modelling the likelihood of statin use at baseline as a function of the above variables using a logistic regression models. The predicted log ORs resulting from this model were used at propensities. We used these propensities in the Matching package (Sekhon, 2011) in R to implement a 1 to 1 matching scheme where all baseline statin users were matched with a single baseline non-user with the nearest propensity for statin use. The PSM data set was then fit to a conditional logistic regression model grouping on matched pairs. All statistical analyses were completed using SAS 9.3 (SAS Institute, Cary, NC USA) or R 3.1.0 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

The baseline characteristics of the study cohort are presented in Table 1A, stratified by use of statins at baseline. In general, statin users were older, had higher BMI distributions, and were more likely to have a current health-care provider. Other baseline characteristics were similarly distributed between the two groups. At baseline, 7.5% of the cohort used statins (8.1% in OS and 6.7% in CT); this increased to 13.5% in the OS at year 3 and 18.6% in the CT at year 6 (Table 1B). At baseline, the most commonly used statins in the WHI OS + CT were simvastatin (30.7%), followed by lovastatin (27.5%), pravastatin (22.3%), fluvastatin (12.0%), and atorvastatin (8.2%) (Table 2). Cerivastatin and rosuvastatin were not used at baseline (not on the market at that time) but were reported in follow-up questionnaires in subsequent years. Low potency statins were used by 39.0% of the cohort, compared with 22.2% for medium potency statins, and 38.8% of the cohort for high potency statins. Lipophilic statins were used by 69.8% of the cohort. The distribution of statin use characteristics was similar among OS and CT participants.

Table 1B. Percentage of WHI OS + CT cohort reporting statin use at study year

Cohort	Baseline (%)	Year 1 (%)	Year 3 (%)	Year 6 (%)	Year 9 (%)
OS + CT	7.5%	9.5%	12.9%	18.6%	5.1%
OS	8.1%		13.5%		
CT	6.7%	9.5%	12.2%	18.6%	5.1%

Abbreviations: CT = Clinical Trial; OS = Observational Study; WHI = Women's Health Initiative. *Note*: WHI OS followed until Year 6 ayd WHI CT followed until Year 9 because of study close-out.

Table 2. Baseline statin use characteristics of the WHI OS + CT

	OS (*N* = 75 243)		CT (*N* = 55 202)		OS + CT (*N* = 131 872)	
Statin use at baseline	6054	8.1%	3665	6.7%	9719	7.5%
Type						
Atorvastatin	564	9.3%	229	6.2%	793	8.2%
Fluvastatin	722	11.9%	446	12.2%	1168	12.0%
Lovastatin	1565	25.9%	1104	30.1%	2669	27.5%
Pravastatin	1349	22.3%	819	22.3%	2168	22.3%
Simvastatin	1873	30.9%	1106	30.2%	2979	30.7%
Cerivastatin	0	0.0%	0	0.0%	0	0.0%
Rosuvastatin	0	0.0%	0	0.0%	0	0.0%
Potency						
Low	2273	37.6%	1521	41.5%	3794	39.0%
Medium	1345	22.2%	811	22.1%	2156	22.2%
High	2436	40.2%	1333	36.4%	3769	38.8%
Category						
Lipophilic	4150	68.6%	2638	72.0%	6788	69.8%
Other	1904	31.5%	1027	28.0%	2931	30.2%
Duration						
<1 year	1898	31.4%	1294	35.3%	3192	32.8%
1–<3 years	2062	34.1%	1213	33.1%	3275	33.7%
3–<5 years	1016	16.8%	598	16.3%	1614	16.6%
5+ years	1078	17.8%	560	15.3%	1638	16.9%

Abbreviations: CT = Clinical Trial; OS = Observational Study; WHI = Women's Health Initiative. *Notes*: Cerivastatin and rosuvastatin are classified as high potency statins. Cerivastatin was classified as lipophilic and rosuvastatin as other. Neither statin was used by the cohort at baseline but both are reported in subsequent years.

In our study cohort, any use of statins (primary hypothesis, as a time-varying variable) in the random-effects logistic regression model was associated with significantly increased NMSC incidence (OR 1.21; 95% CI: 1.07–1.35; Table 3). Secondary analyses were adjusted for multiple testing using the Bonferroni correction method as described in the Materials and Methods section. For the secondary hypothesis of statin type, increased risk was found only for lovastatin (OR 1.52; 95% CI: 1.08–2.16) and simvastatin (OR 1.38; 95% CI: 1.12–1.69). Low (OR 1.33, 95% CI: 1.02–1.74) and high potency statins (OR 1.20; 95% CI: 1.06–1.37) had an increased risk compared with non-statin users. Additionally, lipophilic statin users had a significant increase compared with non-statin users (OR 1.39; 95% CI: 1.18–1.64). There was no clear trend in duration of use; participants using statins for <3 years had a significant increase in odds of NMSC compared with never users; however, those using statins for >3 years were not significantly different compared with never users. In the secondary analyses, there was no statistically significant effect modification found for the relationship between any statin use and NMSC incidence for the prespecified subgroup (age, BMI, smoking, Langleys, vitamin D; Table 4).

As a *post hoc* sensitivity analysis, we conducted a PSM analysis to reanalyse the relationship between statin use and NMSC

Table 3. ORs ratios for NMSC and statin use in the WHI OS + CT

			Age and study arm adjusted			Multivariable-adjusted		
Statin use variable	**Cases**	**Incidence per 1000 person-years**	**OR**	**95% CI**	***P*-value**	**OR**	**95% CI**	***P*-value**
Any statin use[a]					0.101			0.002
No	10026	14.0	Ref			Ref		
Yes	1529	15.6	1.09	0.98–1.21		**1.21**	**1.07–1.35**	
Type of statin					0.400			0.080
None	10026	14.0	Ref			Ref		
Atorvastatin	514	15.4	0.99	0.85–1.16		1.10	0.93–1.30	
Fluvastatin	113	14.0	0.94	0.64–1.39		1.03	0.68–1.56	
Lovastatin	192	15.6	**1.46**	**1.06–2.01**		**1.52**	**1.08–2.16**	
Other[b]	33	17.9	0.90	0.49–1.66		0.90	0.47–1.72	
Pravastatin	241	15.4	0.99	0.76–1.29		1.05	0.78–1.39	
Simvastatin	436	16.3	**1.25**	**1.03–1.51**		**1.38**	**1.12–1.69**	
Statin potency					0.944			0.044
None	10026	14.0	Ref.			Ref.		
Low	305	15.0	1.22	0.97–1.54		**1.33**	**1.02–1.74**	
Med	241	15.4	0.99	0.77–1.27		1.05	0.79–1.40	
High	983	15.8	1.09	0.96–1.22		**1.20**	**1.06–1.37**	
Statin category					0.108			0.001
None	10026	14.0	Ref.			Ref.		
Lipo	772	15.8	**1.22**	**1.05–1.41**		**1.39**	**1.18–1.64**	
Other	757	15.4	0.99	0.87–1.14		1.10	0.95–1.28	
Duration of use					1.000			0.116
None	10026	14.0	Ref.			Ref.		
<1	417	15.3	1.12	0.94–1.33		**1.22**	**1.01–1.49**	
1–<3	558	15.7	1.11	0.95–1.29		**1.23**	**1.04–1.47**	
3–<5	291	15.6	1.01	0.82–1.24		1.11	0.88–1.38	
5+	263	15.8	1.10	0.88–1.37		1.23	0.97–1.57	

Abbreviations: BMI = body mass index; CI = confidence interval; CT = Clinical Trial; NMSC = non-melanoma skin cancer; OR = odds ratio; OS = Observational Study; WHI = Women's Health Initiative. Fully adjusted models were adjusted for age, study arm, educational attainment, BMI, smoking history, vitamin D consumption, sun exposure, physical activity, health-care provider, occupation, and hormone use history. Bold denotes significance.

[a]Statin use is the primary hypothesis, tested at $\alpha = 0.05$. Analyses on statin type, potency, category, and duration were secondary hypotheses and adjusted for multiple testing using the Bonferroni method.

[b]Includes cerivastatin and rosuvastatin. These statins were used by a very small percentage of women and never at baseline.

Table 4. Effect modification for NMSC incidence and any statin use

Effect modifier	***P*-value**
Age	0.353
BMI	0.388
Smoking	0.979
Langleys	0.326
Vitamin D category	0.063

Abbreviations: BMI = body mass index; NMSC = non-melanoma skin cancer.

incidence, as detailed in the Materials and Methods section. This analysis matched women who used statins with women who did not use statins (but had a similar propensity to use statins), and compared the outcomes between the matched pairs. The PSM analysis was based on 'any statin use' and cohort characteristics at study baseline, and did not find a significant relationship between NMSC incidence and statin use.

DISCUSSION

In our large cohort of postmenopausal white women, use of statins was associated with an increased incidence of all NMSC. In particular, after adjusting *P*-values to account for testing of multiple secondary hypotheses on statin type and potency, increased risk was found for lovastatin and simvastatin statin types only, which was consistent with our finding of an increased risk for lipophilic statins, low potency, and high potency statins. There was no clear association for duration of use. There was also no significant effect modification for the relationship between NMSC and statin use by age, BMI, smoking, Langleys, vitamin D use, or history of NMSC/melanoma. To our knowledge, this is the first study to examine the relationship between statin use and all NMSC in a prospective cohort setting.

Comparison with other studies. The first two simvastatin trials suggested an association with NMSC seen more often in treatment groups (Mascitelli *et al*, 2010). Other prior clinical studies on the relationship between NMSC and statins have been somewhat limited and conflicting, ranging from no significant relationship (for either all NMSCs or BCC/SCC) (Bjerre and LeLorier, 2001; Asgari *et al*, 2009; Haukka *et al*, 2010; Li *et al*, 2014), increased risk with statin use (Scandinavian Simvastatin Survival Study Group., 1994; Collins *et al*, 2002; Kuoppala *et al*, 2008; Arnspang *et al*, 2014), to decreased risk with statin use (Blais *et al*, 2000; Graaf *et al*, 2004; Peto *et al*, 2008). Few prospective studies have been conducted to investigate the relationship between statin use and either BCC or SCC, particularly with as many participants and cases as our study. However, several large studies have suggested an increased risk of NMSC associated with statin use. One study that showed an increased risk with statin use and NMSC incidence was a meta-analysis of all cancers and statins (median RR 1.6, range 1.2–2, evidence strength moderate) (Kuoppala *et al*, 2008); this analysis included RCTs, cohort studies, and case–control studies. It was also reported that NMSC was observed more often in the treatment groups of two simvastatin trials, the Scandinavian

Simvastatin Survival Study (4S) and the Heart Protection Study (HPS), with the relationship statistically significant if both studies were combined (Scandinavian Simvastatin Survival Study Group, 1994; Collins *et al*, 2002) This agrees with our finding of a substantial increase in NMSC risk being seen for simvastatin specifically. One record-linkage study of over 400 000 Finnish participants did not find an overall association with statin use and NMSC, but found an increased risk associated with pravastatin specifically (Haukka *et al*, 2010). A nationwide case–control study in Denmark also found significantly increased risk of BCC only with ever statin use among 38 484 cases (OR 1.09; 1.06–1.33), which the authors attributed to possible residual confounding (Arnspang *et al*, 2014). A prior WHI analysis found no significant evidence for statin use as a risk factor for melanoma (Jagtap *et al*, 2012). In addition to these reports, the relationship of NMSC with statin use has been assessed in retrospective and case–control studies with mixed results (Blais *et al*, 2000; Graaf *et al*, 2004; Asgari *et al*, 2009; Haukka *et al*, 2010; Arnspang *et al*, 2014).

One plausible biological mechanism for increased NMSC risk with statin use is immunomodulation leading to increased regulatory T cells (Curiel, 2007; Jang, 2008; Mausner-Fainberg *et al*, 2008; Goldstein *et al*, 2009a,b). However, multiple molecular pathways have also been proposed for how statins could decrease NMSC risk (Cooper *et al*, 2003; Gniadecki, 2004; Wu *et al*, 2004; Corcoran and Scott, 2006; Tang *et al*, 2007; Von Hoff *et al*, 2009), and alternative biological mechanisms warrant further study. The literature has also reported photosensitivity and cutaneous side effects associated with statins, which may be related to increased NMSC risk, although the mechanisms are also not well understood (Rodriguez-Pazos *et al*, 2010; Nardi *et al*, 2011; Toth *et al*, 2012).

Sensitivity analysis. In a *post hoc* PSM analysis conducted as a sensitivity analysis, the use of statins was no longer found to be significantly associated with NMSC incidence. However, the PSM analysis examined outcomes of matched pairs based on a propensity to use statins rather than statin use itself. In contrast, the main analysis, which investigated actual statin use and adjusted for measures of health access, found a significant relationship between NMSC incidence and statin use. Additionally, the PSM analysis was based on characteristics at study baseline; however, statin use increased considerably during the course of the trial, which was accounted for in the main analysis only. The conflicting findings of the main analysis with the PSM analysis suggest other possible contributors to our findings of increased NMSC incidence with statin use, which may be related to characteristics of women with a propensity to use statins (including better medical surveillance and access to care). However, our main analysis and our sensitivity analysis using PSM accounted for measures of socioeconomic status including current health-care provider and education. A randomised trial of statin use would control for such characteristics of users and non-users.

Strengths and limitations. The strengths of this study include the large size and geographic distribution of cohort, prospective nature of the study (given the rarity of prospective studies on this relationship), large size of the cohort and number of NMSC cases, and detailed information on confounders and exposures including statin use (including duration and type). Although factors such as age, BMI, smoking, solar irradiance, and vitamin D intake did not significantly modify the relationship of NMSC with statin use, the fact that our study took these into account is another strength. Limitations of the study include the fact that the study was observational in nature, NMSC was self-reported (not centrally adjudicated) and not further broken down into BCC and SCC, time to event data was not collected, and statin use was self-reported and relatively low at baseline. In addition, we limited the analyses to white women because of the small sample size (and thus potential number of NMSC cases) in other ethnicities, limiting generalisability of the findings to ethnicities where NMSC is not as prevalent. We were also not able to fully adjust for sun exposure because of limitations in the data collection, but we adjusted for proxies of exposure including Langleys and geographic area. Additionally, the lack of duration–effect relationship found for statin use and NMSC incidence (particularly effect found for those treated <1 year) points to the possibility of residual confounding.

CONCLUSIONS

In conclusion, the use of statins was associated with increased NMSC risk in our cohort of postmenopausal white women. As statin use is likely to increase significantly in the future under the new statin use guidelines and NMSC is already the most common cancer in the United States, these results may be important and warrant further investigation. As these observations do not provide evidence of causality or that a side effect of statin use is increased NMSC, we are not suggesting changes in current statin recommendations. Regardless, preventive sun exposure measures (which have been shown to be protective against NMSC) should be recommended for statin users as well as non-users (including sunscreen, wearing protective clothing, and avoiding the sun during peak exposure times). Patients at high risk for NMSC because of personal/family history, medical comorbidities, or skin type may want to consider using a statin type that is less strongly associated with NMSC incidence. Further areas for investigation include studying this relationship in the setting of a randomised controlled trial (including the effects of specific statin types on BCC and SCC separately), the effect of protective sun exposure behaviors on this relationship, and the underlying biological mechanisms that may mediate increased NMSC risk from statin use.

ACKNOWLEDGEMENTS

We acknowledge the dedicated efforts of investigators and staff at the WHI clinical centres, the WHI Clinical Coordinating Center, and the National Heart, Lung, and Blood program office (listing available at http://www.whi.org). We also recognise the WHI participants for their extraordinary commitment to the WHI program. The WHI program is funded by the National Heart, Lung, and Blood Institute, National Institutes of Health, US Department of Health and Human Services through contracts HHSN268201100046C, HHSN268201100001C, HHSN268201100002C, HHSN268201100003C, HHSN268201100004C, and HHSN271201100004C. The funders had no role in design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. The WHI is registered under ClinicalTrials.gov. Trial registration ID: NCT00000611. This study was approved by the ethics committees at the WHI Coordinating Center, Fred Hutchinson Cancer Research Center, and all 40 clinical centres.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

AW, MS, MD, and JT participated in study conception and design. KK, HH, and MD performed the data analysis. AW, MS, MD, and JT participated in initial data interpretation. AW wrote the initial draft of the manuscript. All authors contributed to additional data interpretation and revisions and approval of the manuscript.

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